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EXPERIMENTS ON FACTORS THAT INFLUENCE MUSCULAR FUNCTION 1/1
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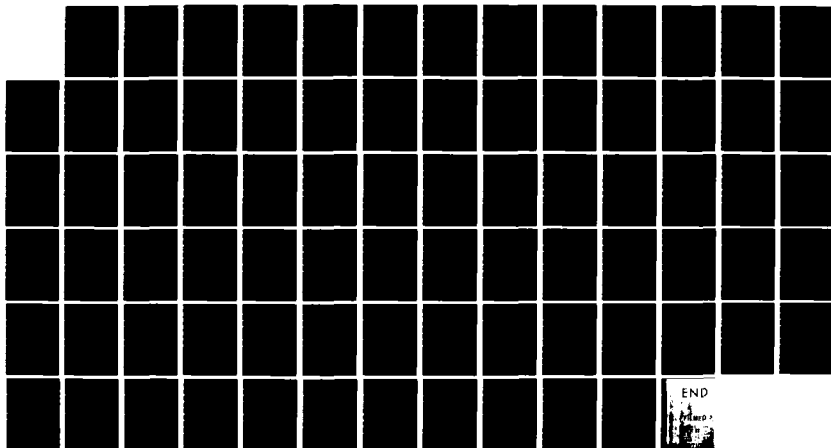
A R LIND ET AL. 25 MAY 83 AFOSR-TR-83-0859

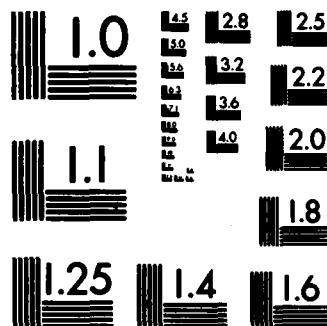
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) 1. <u>Circulatory control during isometric contractions</u> These two years of work were concerned with muscular function and fatigue. In the past we have contributed heavily to the current good understanding of the physiological responses to sustained isometric contractions and the development of fatigue. But what of intermittent isometric contractions, where our contributions are the only ones available? The systemic cardiovascular responses are much the		

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same when the contractions result in muscular fatigue, at which time the mean blood pressure is the same as it is in response to sustained isometric contractions. All the available evidence points to the same mechanisms being involved, centering around the reflex of chemical origin in active muscles.

There appears, however, to be considerable differences in the local control of blood vessels when isometric contractions are pursued to fatigue on a continuous or on an intermittent basis. Following continuous contraction, the blood flow through the muscles is habitually very high and probably maximal, irrespective of the tension exerted. In contrast, following fatigue induced by intermittent isometric contractions where, for example, the bouts of contraction were at 60% of maximal strength for 4 seconds, with 8 seconds interval between them, the blood flow through the forearm was just over half the maximal value, despite the fact that the pressor response continued to increase to a mean arterial blood pressure of about 150 mmHg at the point of muscular fatigue. Clearly, some vasoconstrictor response was intervening since the blood flow remained constant throughout a large portion of the experimental duration in the face of a steadily increasing pressure.

In the present experiments we have shown that the constriction is neural in origin and that metabolites which normally inhibit that constriction are unable to migrate through the interstitial space to larger arterioles not in the direct vicinity of the contracting muscles. Thereby, for the first time it is clear that sympathetic constriction applies to the active muscles as well as to inactive tissues and that during strong intermittent isometric contractions is not successfully inhibited by locally released metabolites. Further research may provide answers as to the most economical management of intermittent isometric forces to avoid fatigue.

2. The influence of rhythmic exercise on isometric strength and endurance

It is easy to understand the importance of experiments such as have been performed here. In practical terms it is common for individuals to be engaged in rhythmic or predominantly rhythmic exercise, followed by isometric functions such as lifting, exerting leverage forces, etc. The information we have generated create a picture of some alarm and of great interest in both practical and physiological terms. The performance of very short bouts of rhythmic exercise can result in dramatic reductions of isometric endurance and, to some extent, isometric strength. The functional consequences are obvious: jobs calling for either isometric strength or endurance can be seriously impaired by previous rhythmic exercise.

The causes are only partially disclosed by our experiments. It is obvious that the increase in muscle temperature with continued rhythmic exercise has a part to play in the reduction of muscular endurance. But other events have a part to play and their origin is uncertain. It seems reasonable to believe that metabolic factors may be implicated but problems of neurotransmission or recruitment of motor units cannot be excluded. With such large reductions in isometric muscular function, which may be exacerbated, for example, by hot environmental conditions, the matter has considerable practical interest. It is easy to envisage accidents arising from the practical equivalents of our experimental conditions; it is equally feasible to envisage further work to minimize or eradicate the profoundly deleterious influence of rhythmic exercise on isometric muscular function.

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Items b) and c): See accompanying report entitled "EXPERIMENTS ON FACTORS THAT INFLUENCE MUSCULAR FUNCTION IN MAN", by A.R. Lind, C.A. Williams and M.D. Hoffman.

d) Publications resulting from A.F. Contract:

The blood pressure response during isometric exercise in fast and slow twitch skeletal muscle in the cat. J.S. Petrofsky and A.R. Lind. Europ. J. Appl. Physiol. 44: 233-230, 1980.

The influence of temperature on the isometric characteristics of fast and slow twitch muscle in the cat. J.S. Petrofsky and A.R. Lind. Pflugers Arch. 398: 149-154, 1981.

The influence of fiber composition, recruitment order and muscle temperature on the pressor response to isometric contractions in skeletal muscle in the cat. J.S. Petrofsky, C.A. Williams, and A.R. Lind. Circ. Res., Suppl. I, 48: 32-36, 1981.

The influence of temperature on the amplitude and frequency components of the EMG during brief and sustained isometric contractions. J.S. Petrofsky and A.R. Lind. Europ. J. Appl. Physiol. 44: 198-208, 1980.

Some of the physiological responses to isometric contractions and the mechanisms that control them. A.R. Lind. Proceedings of XXVII International Congress of Physiology. Adv. Physiol. Sci. 18: , 1980.

The effect of deep muscle temperature on the cardiovascular responses of man to static effort. J.S. Petrofsky, R. Burse, and A.R. Lind. Europ. J. Appl. Physiol. 47: 7-16, 1981.

The effect of hand-grip span on isometric exercise performance. J.S. Petrofsky, C.A. Williams, G. Kamen, and A.R. Lind. Ergonomics 23: 1129-136, 1980.

The isometric strength and endurance of men and women. C.A. Williams, J.S. Petrofsky, and A.R. Lind. In Preparation.

The relationship of isometric strength and endurance as fatigue develops. C.A. Williams, J.S. Petrofsky, and A.R. Lind. In Preparation.

The blood flow through the "resting" arm during hand-grip contractions. A.R. Lind, T.E. Dahms, C.A. Williams, and J.S. Petrofsky. Circ. Res. 48 (Suppl. 1): 104-108, 1981.

The forearm blood flow during intermittent hand-grip isometric exercise. C.A. Williams, J.G. Mudd, and A.R. Lind. Circ. Res. 48 (Suppl. 1): 110-117, 1981.

Neural and metabolic control of forearm blood flow during brief isometric contractions. A.R. Lind, J.G. Mud, and C.A. Williams. In preparation.

The influence of rhythmic exercise on isometric endurance. M.D. Hoffman, C.A. Williams, and A.R. Lind. In preparation.

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The effect of rhythmic exercise on muscle temperature and isometric endurance. M.D. Hoffman, C.A. Williams and A.R. Lind. The Physiologists, 24: 63, 1981.

The effect of diprydamole on the concentration of ATP during sustained isometric exercise. Williams, C.A. and A.R. Lind. Federation Proceedings. 41: 1270, 1982.

e) Professional Personnel:

A.R. Lind, D. Phil., D. Sc.

C.A. Williams, Ph.D.

M.D. Hoffman, M.D. (Dr. Hoffman, a medical student, received the M.D. degree on 14 May, 1983)

- f) i) Spoken papers given at AFOSR FASEB and Physiological Society meetings
ii) Consultation by telephone and in person by Dr. Burns from the US School of Aerospace Medicine concerning the development of muscular fatigue in pilots of high performance aircraft as a result of performing the MI manoeuvre.

g) Not applicable

- h) See Abstract (item a) above) and final report (items b) and c) above).

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EXPERIMENTS ON FACTORS THAT INFLUENCE
Muscular ~~muscle~~ FUNCTION IN MAN

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I. ASSESSMENT OF THE COMPETITION BETWEEN METABOLIC DILATION, NEURAL
CONSTRICTION AND MECHANICAL OBSTRUCTION TO THE BLOOD FLOW SUPPLYING
MUSCLES DURING INTERMITTENT, ISOMETRIC CONTRACTIONS:

In earlier experiments we had shown that following brief isometric contractions, there was a linear increase in the subsequent blood flow through the muscles up to a tension of about 60% of the maximal voluntary contraction (MVC), but that further increases in the isometric force exerted resulted in no further increase in the local blood flow (Lind & Williams, 1979). Also, we could find no evidence, in an exhaustively systematic series of experiments, that a myogenic response of the local blood vessels in the forearm existed in these circumstances. Instead, all of the dilation observed could be explained in terms of local release of dilator metabolites while the reason for the failure to increase the local blood flow at forces in excess of 60% MVC was left open to speculation. It is also known that at tensions of about 60% MVC there is complete mechanical occlusion of the local blood supply during the contraction. The only other known influences are neural in nature. The α -adrenergic neurons are under sympathetic nervous control and such neural traffic is known to increase during muscular exercise, its effective resultant widespread vasoconstriction increasing with the severity of the muscular activity. It is not known whether the vasoconstriction also applies to the working muscles; it is presumptive from the work of Verghaegh et al (1977) that any local release of norepinephrine from α -adrenergic endings is inhibited locally by many of the metabolites released from exercising skeletal muscle. The β -adrenergic neurons in the vessel walls have no neural connections and are stimulated by circulating epinephrine released from the adrenal glands, the only known source of epinephrine in the body. Once stimulated the β -receptors dilate the blood vessels.

In the present experiments the aims were to assess and explore the metabolic and neural influences on the blood vessels of the muscles of the forearm during and after intermittent isometric contractions.

METHODS

Subjects: Six healthy individuals (aged 23-36 years) volunteered to be subjects in this study; 4 were male and 2 were female. All were physically examined, including an exercise (ECG) stress test and were fully informed of the potential risks involved with the procedures in these experiments. Each signed a statement of informed consent.

Training: All subjects were trained to perform intermittent isometric contractions as described before (Lind & Williams, 1979) using a hand-grip dynamometer (Clark, Hellon & Lind, 1958). The training period required approximately 3 weeks.

MEASUREMENTS

Forearm blood flow: The blood flow through the forearm was measured by strain-gauge plethysmography (Whitney, 1953) with the venous collection cuff inflated automatically for 6 sec every 12 sec to a pressure of 50-55 mm Hg. There were 5 measurements of blood flow.min⁻¹; a wrist-cuff was not used in these experiments (Williams & Lind, 1979). As previously described (Lind & Williams, 1979), the forearm blood flow was measured 2 sec after the release of isometric tension of each of a series of repeated, brief contractions. All blood flows reported here refer only to the flow immediately following each contraction and thereby is taken to reflect the vasodilator effect of the muscular contraction.

During the experiments described below a 20 g teflon catheter was inserted precutaneously into the brachial artery. A Statham pressure transducer was attached to the catheter to allow the direct measurement of blood pressure. Heart rate was measured from a continuous recording of the electrocardiogram.

Plasma catecholamines: The concentrations of arterial and venous plasma catecholamines were measured. The venous blood samples were obtained from a 20 g teflon catheter inserted into the antecubital vein and advanced retrogradely

into the deep venous plexus of the forearm. Venous samples were withdrawn during experiments separate from those involving arterial catheterization. In either case, 5 ml blood were withdrawn from the catheters into ice-chilled test tubes containing ECTA-glutathione and centrifuged at $1000 \times g$ for 20 min at $0-4^{\circ}\text{C}$. Plasma samples were stored at -70°C until assays were performed. Total plasma and differential catecholamines (adrenalin and noradrenalin) were measured by radioenzymatic methods using [^3H]-S-adenosylmethionine and catecholamine-o-methyltransferase (Upjohn Diagnostic) based on a procedure described by Passon & Peuler (1973). Differential characterization of plasma catecholamines was carried out by thin-layer chromatographic separation of tritiated normethanephine and tritiated metanephine.

Osmolarity and electrolytes: Venous plasma osmolarity was determined by the freezing point depression using an Advanced Instruments osmometer.

Arterial and venous Na^+ and K^+ were determined by flame photometry with LiF as the standard.

Adenosine triphosphate (ATP): Venous plasma adenosine triphosphate (ATP) was measured by withdrawing 1-2 ml blood and transferring it immediately into ice-chilled tubes containing 0.1 ml of 0.11 M sodium citrate and centrifuged at $10,000 \times g$ for 15 sec. A 0.2 ml volume of plasma was withdrawn and added to 0.2 ml volume of crude firefly tail extract (Sigma, FLE-50). The initial light signal produced by plasma samples was compared to known amounts of ATP (Forrester & Lind, 1969). The time between the drawing of the venous sample to the measurement of emitted light by the luciferin-luciferase reaction was measured; it averaged 60 sec. Care was taken to avoid hemolysis; any samples showing hemolysis were discarded.

PROCEDURES

The subjects were seated and their arms exposed to the ambient environment ($22-24^{\circ}\text{C}$). At the start of each experiment, the subject exerted 2 consecutive

maximum efforts (each <3 sec) with a 3-min interval between them. The highest tension achieved was regarded as the maximum voluntary contraction (MVC).

During control experiments as well as during experiments involving arterial catheterization, two types of exercise were performed.

Series 1: The forearm blood flow was measured at rest and 2 sec after subjects exerted single, brief isometric contractions at tensions ranging from 10-80% MVC (see Fig. 1, Lind & Williams, 1979). The tension was applied rapidly and held for 2 sec. The forearm blood flow was allowed to return to the resting level before the next tension was applied.

Series 2: The forearm blood flow was measured for 2 min at rest before a series of repeated, consecutive contractions began. Contractions were applied in the "square-wave" manner at a tension of 60% MVC. These contractions were held for a total of 4 sec with 8 sec of relaxation between the successive contractions. Within the 8 sec rest interval, and 2 sec after the release of tension, forearm blood flows were measured (see Fig. 2, Lind & Williams, 1979). Contractions were exerted until fatigue was achieved; fatigue was taken to occur when either the tension could not be achieved or could not be held for 4 sec. The blood flow was measured after each of the contractions. Since the number of contractions needed to achieve fatigue varied from subject to subject, the duration of exercise has been expressed as a percentage of the total number of successive contractions.

The Influence of β -adrenergic Blockade on Forearm Blood Flow: After arterial catheterization, the subjects performed the isometric exercise described in Series 1 and 2. Blood flows were measured with the catheter in place and were used as the control condition. When forearm blood flow had returned to the resting level, a total of 1.0 mg propranolol (INDERAL) in 3 ml saline was infused over a 1 min period. During the infusion, blood pressure, heart rate

and forearm blood flows were measured continuously. Two minutes after the infusion, resting flows were measured for 2 min, followed by a repetition of the experiments described as Series 1 and 2. Heart rates and blood pressure were recorded continuously.

The Influence of α -adrenergic Blockade on Forearm Blood Flow: On separate occasions and following the control experiments of Series 1 and 2, 0.5 mg phentolamine (REGITINE) in 5 ml saline was infused into the forearm over a 5 min period. Blood pressure, heart rate and blood flows were recorded continuously during the infusion. Five minutes after the end of infusion, the experiments as described for Series 1 and 2 were repeated.

In order to examine whether forearm blood flow was mediated by α -adrenergic constrictor influences, phenylephrine was used to challenge the blood flow responses found following infusion of phentolamine. This procedure was carried out on only 3 of the subjects. Following the control experiments of Series 1 and 2, 60-100 ug phenylephrine (NEO-SYNEPHRINE) were infused into the forearm. During the infusion, blood pressure, heart rate and forearm blood flows were measured continuously. All subjects experienced piloerection of the test forearm only. Two minutes after the end of infusion, Series 1 and 2 experiments were repeated. After the blood flow had returned to pre-exercise levels, an additional 50 ug phenylephrine in 1 ml saline were infused into the forearm; 30-60 sec later, 0.5 mg phentolamine in 5 ml saline were infused over a 5 min period. For one of the subjects, this amount of phenylephrine was insufficient to counteract the effects of phentolamine, as readily discernible by the pattern of resting forearm blood flow, which increased immediately 2-3 fold above control resting values. These data were discarded. On another occasion for this subject, a constant infusion of phenylephrine was used at a rate of 50 ug per 5 min during the injection of phentolamine and the subsequent exercise.

RESULTS

Influence of Sympathetic Adrenergic Blocking Agents on Post-contraction Blood Flow During Brief Contractions

Series 1: When subjects exerted a single hand-grip contraction held for only 2 sec at tensions ranging from 10 to 80% MVC, in the control experiments there was a direct relationship between the first post-contraction forearm blood flow and the tension up to 60% of the subjects' MVC. Thereafter, even though the tension of the next contraction exceeded 60% MVC, there was no further increase in the first post-contraction flow. This relationship is shown in Fig. I.1 during the control conditions, when a catheter was indwelling in the brachial artery of the exercising arm. Forearm blood flow increased to $14.9 \pm 1.7 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$ at its highest level following 2 sec contractions at 60 and 80% MVC. The hyperbolic pattern of response between blood flow and tension was quite similar in absolute blood flows to those shown previously in 11 subjects where no catheter was in place (see Fig. 3, Lind & Williams, 1979).

The same hyperbolic relationship with almost the same absolute blood flows resulted when subjects performed 2 sec contractions following administration of 1.0 mg propranolol. These data are shown also in Fig. 1, and it can be seen that the highest post-contraction blood flow attained after tensions of 60 and 80% MVC was 13.3 ± 1.5 and $13.8 \pm 1.4 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$. There was no difference between the blood flows measured during the control conditions and after infusion of the β -blocker propranolol at any given tension ($P > 0.05$).

The resting forearm blood flow increased abruptly within 3 sec of the infusion of phentolamine into the brachial artery, to reach an average value of $10.9 \pm 1.6 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$. Following each of the brief contractions the blood flow showed a direct, linear relationship with tension (Fig. I.1). While maximal forearm blood flows were not expected in response to contractions

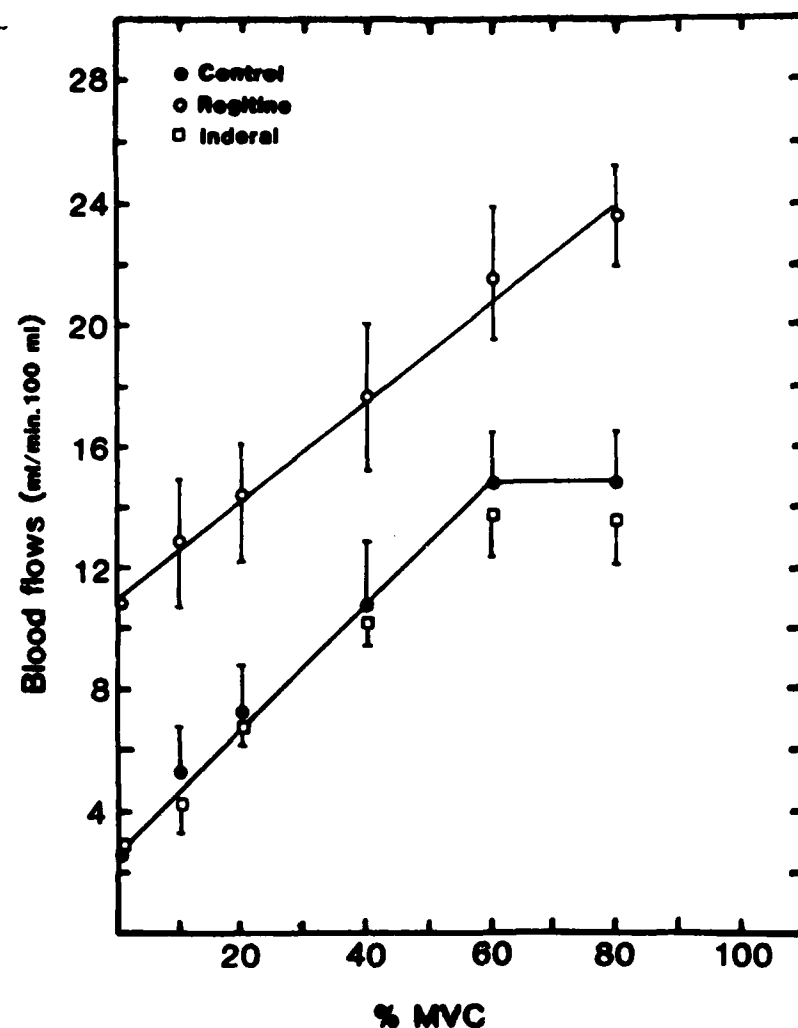


Figure 1.1: The change in the blood flow measured in response to single contractions exerted for 2 sec at various tensions. All flows were measured 2 sec after the release of tension. Each point represents the average blood flow in $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$ measured from 5 subjects. The bars represent the sem of the results. Contractions were exerted during control conditions (O) and following the arterial infusion of either 0.5 mg phentolamine (O) or 1.0 mg propranolol (\square).

lasting only 2 sec, blood flow did reach the high level of 23.9 ± 1.7 ml.min⁻¹.100 ml⁻¹ following contractions at 80% MVC. This result was somewhat surprising because there were no systemic indications (i.e., increases in blood pressure or heart rate) that a change in sympathetic adrenergic activity occurred during these very brief isometric contractions which were not fatiguing in nature. The slopes of the curves relating blood flow to tension in all 3 experiments illustrated in Fig. I.1 were not different from each other.

Series 2: Isometric contractions at 60% MVC were exerted repetitively for 4 sec in duration every 12 sec. This exercise was continued until fatigue was reached and was performed twice by each subject for each experiment: first, contractions were exerted with the catheter in place and then after the infusion of either 0.5 mg phentolamine, or on separate occasions, 1.0 mg propranolol. The average duration of the exercise performed for the first time during each experiment was 494 ± 62.3 sec. As shown in Fig. I.2, there was no difference between the forearm blood flows during control conditions, or after the infusion of propranolol, 2.9 ± 0.6 and 2.7 ± 0.7 ml.min⁻¹.100 ml⁻¹, respectively. As exercise continued, there was a steadily increasing mean arterial blood pressure, as shown in the upper panel of Fig. I.2, reaching levels of 172 ± 48 mm Hg at the point of fatigue. In spite of this large increase in perfusion pressure, the blood flows measured during the 8 sec rest intervals between successive contractions never reached levels greater than 23.5 ± 1.4 during control conditions and 25.9 ± 3.3 ml. min⁻¹.10ml⁻¹ in the presence of propranolol. Resistance decreased from a resting value of 39.4 ± 17.6 PRU to 5.1 ± 0.06 PRU early in the series of contractions and thereafter gradually increased to 6.6 ± 1.1 PRU. As indicated previously (Lind & Williams, 1979) these blood flows represent approximately half the maximum flow possible in the human forearm.

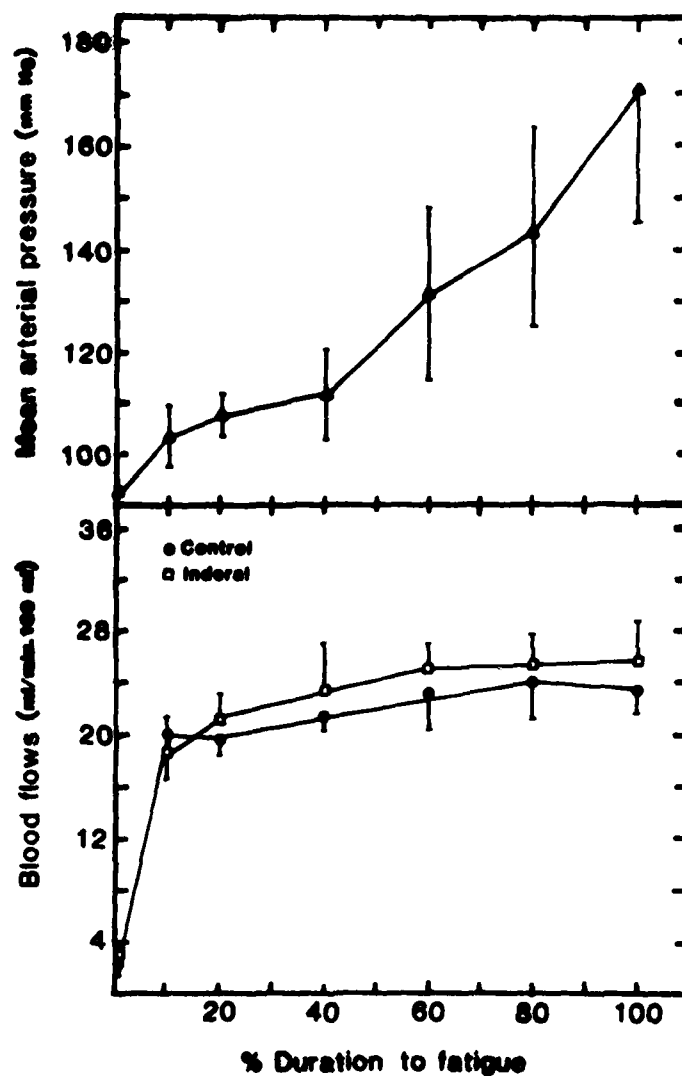


Figure I.2: The changes in mean arterial blood pressure (mm Hg) as shown in the top panel, forearm resistance, calculated in PRU, as shown in the middle panel, and forearm blood flow ($\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$), shown in the lower panel, during a series of contractions at 60% MVC held for 4 sec until fatigue occurred. The points represent the average results from 5 subjects \pm sem. There were 8 sec of relaxation between each successive contraction. Mean pressure was calculated as the diastolic pressure plus one third of the pulse pressure. The total time taken to develop fatigue was normalized. Blood flows are shown from contractions that were carried out during control conditions (O) and following infusion of 1.0 mg propranolol (□).

When successive intermittent contractions at 60% MVC were exerted following infusion of phentolamine, forearm blood flow increased progressively as fatigue was approached. These results are shown in Fig. I.3. In the control conditions, blood flow quickly reached levels of $19.8 \pm 1.3 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$ in the early part of exercise, but did not significantly increase for the remainder of exercise, reaching levels of only $23.2 \pm 2.1 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$ at fatigue. However, after the forearm vasculature had been exposed to the α -blocking agent, phentolamine, resting blood flows increased immediately, as the infusion began, to $8.9 \pm 1.6 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$ from resting levels of $2.8 \pm 0.6 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$, during control conditions. When intermittent contractions were exerted to fatigue, blood flow increased continuously and followed the change in the mean pressure (see Fig. I.3). Blood flows reached their highest levels at fatigue and averaged $38.7 \pm 1.4 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$, a level that is at or approximate to the maximal value. Resistance on the other hand decreased from resting levels of $13.1 \pm 1.7 \text{ PRU}$ following infusion of phentolamine, and then remained constant for the duration of exercise, ranging from 4.9 to 4.8 PRU.

On separate occasions, 50-100 ug phenylephrine, an α -adrenergic agonist, was infused into the brachial artery before the α -antagonist drug phentolamine was infused. This was done in an attempt to challenge the α -blockade accomplished by phentolamine and thereby verify that blood flow had attained its maximal levels in the forearm by blockade of sympathetic α -adrenergic mechanisms. This procedure was attempted on 3 subjects and the results are summarized in Table I.1. Infusion of phentolamine or phenylephrine did not affect the increase in mean arterial blood pressure, which reached the same high levels at fatigue in all these experiments. In each of the conditions described in Table 1 the resistance, calculated for the forearm, increased at an

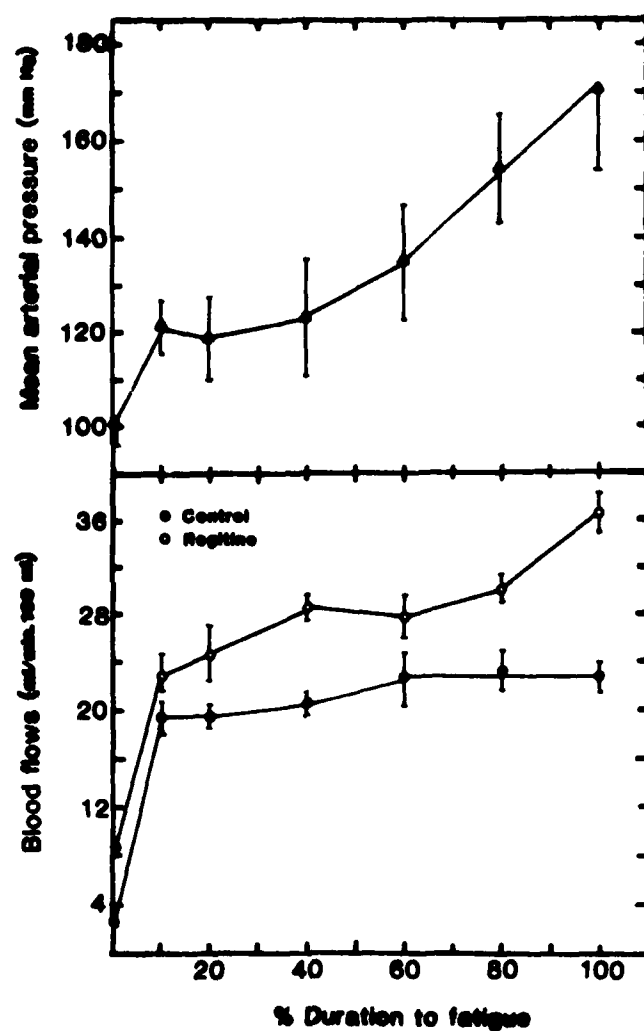


Figure I.3: The changes in mean pressure (mm Hg), forearm resistance (PRU) and forearm blood flow ($\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$) during a series of intermittent contractions exerted at 60% MVC. Each contraction was held for 4 sec and there were 8 sec of relaxation between successive contractions. Blood flows were measured during the relaxation period, 2 sec after the release of tension. Exercise was carried out during control conditions (O) and following the infusion of 0.5 mg phentolamine (O). Each point represents the average from 5 subjects \pm sem.

TABLE 1 Effects of Phenylephrine on Changes in Mean Arterial Blood Pressure and Forearm Blood Flows During Fatiguing Intermittent Contractions at 60% MVC

	Control			Phenylephrine			Phenylephrine + Phentolamine		
	MABP	FBF	R	MABP	FBF	R	MABP	FBF	R
Rest	(mmHg) 91 ± 4.9	(ml.min ⁻¹ .100 ml ⁻¹) 1.9 ± 0.52	(PRU) 47.9	(mmHg) 97 ± 4.6	(ml.min ⁻¹ .100ml ⁻¹) 1.1 ± 0.2	(PRU) 88.1	(mmHg) 90 ± 5.0	(ml.min ⁻¹ .100 ml ⁻¹) 5.5 ± 1.3	(PRU) 16.3
20% Duration	101 ± 8.4	21.3 ± 1.7	4.7	104 ± 4.0	19.7 ± 1.3	5.4	111 ± 1.6	22.1 ± 2.2	5.0
40% Duration	116 ± 5.3	21.5 ± 2.8	5.4	111 ± 1.9	21.9 ± 1.7	5.0	113 ± 7.3	22.4 ± 3.0	5.0
60% Duration	124 ± 5.8	23.8 ± 2.6	5.2	113 ± 2.9	22.9 ± 3.0	4.9	133 ± 15.1	22.8 ± 2.6	5.8
80% Duration	142 ± 11.2	23.6 ± 2.2	6.0	133 ± 8.4	22.3 ± 2.2	5.9	140 ± 11.3	25.3 ± 2.7	5.5
100% Duration	177 ± 23.7	22.9 ± 1.7	7.7	167 ± 16.5	22.3 ± 2.9	7.5	162 ± 21.0	21.4 ± 2.7	7.6

values are ± SEM

identical rate throughout the fatiguing exercise. Forearm blood flows were similar during both the control experiments and those following infusion of phenylephrine, reaching $22.9 \pm 1.7 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$ and $22.3 \pm 2.9 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$, respectively, at fatigue. When phentolamine was infused after its agonist phenylephrine, the forearm blood flow did not achieve maximal levels at fatigue as was the case with phentolamine alone, but stayed in a steady-state ranging from 22 to 25 $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$. This level of blood flow was the same as that seen during exercise in both the control and phenylephrine conditions.

Changes in Vasoactive Metabolites During Fatiguing Intermittent Contractions

In order to assess the interaction between changes in sympathetic adrenergic activity and exercise induced metabolic vasodilatation, venous blood samples were withdrawn from the deep venous plexus of the contracting forearm. Plasma samples were analyzed for changes in metabolites known to cause skeletal muscle vasodilatation. Table I.2 lists the changes measured in venous plasma osmolarity (mosmol) for 5 subjects exerting intermittent hand-grip contractions at 60% MVC to fatigue. The time taken to achieve fatigue has been normalized for each subject so that comparisons can be made. As exercise proceeded there was little or no increase in the osmolarity of the venous blood. The resting value, $293 \pm 1.5 \text{ mosmol}$ was not significantly different from those during exercise, averaging $305 \pm 2.0 \text{ mosmol}$ in the early stages of exercise and $302 \pm 9.2 \text{ mosmol}$ at the end of the exercise.

Figure I.4 shows the changes of K^+ efflux that occurred in response to intermittent isometric contractions. The efflux was calculated from the product of forearm blood flow and the concentration of K^+ ion in the venous plasma. Since it was shown in Figs. I.1 and I.2 that blood flow increased in response to

the first few contractions to a steady-state level averaging 23.5 ± 1.4 $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$, the increase in K^+ efflux effects the changes in K^+ concentration in the venous plasma of the exercising forearm as well as the steady state forearm blood flow. The concentration of K^+ increased from

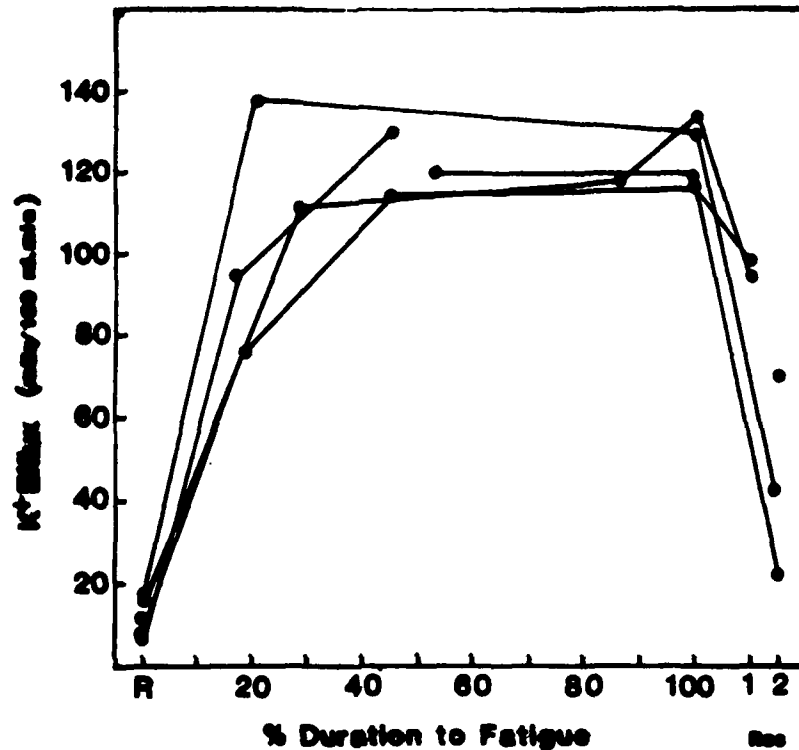


Figure 1.4: The change in the K^+ during intermittent contractions at 60% MVC held for 4 sec with 8 sec rest. Each curve represents the increases in K^+ concentrations (in $\text{mEq} \cdot \text{L}^{-1}$) multiplied by the forearm blood flow (in $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$) to give the pattern of efflux for 5 subjects. Venous blood flow samples were withdrawn from a catheter inserted retrogradely into the deep venous plexus in the forearm. The concentrations of K^+ at rest were $3.6 \pm 0.15 \text{ mEq} \cdot \text{L}^{-1}$; these increased to $4.9 \pm 0.22 \text{ mEq} \cdot \text{L}^{-1}$ by 20% duration of the fatiguing exercise and thereafter remained constant until contractions were stopped.

TABLE 2 Changes in Venous Plasma Osmolarity During
Fatiguing Intermittent Contractions at 60% MVC

Subject	Rest	Percentage Duration to Fatigue					Recovery	
		20%	40%	60%	80%	100%	1 min	
A	292 m-osmol	303 m-osmol	305 m-osmol	302 m-osmol	298 m-osmol	289 m-osmol	293 m-osmol	
B	292	303	306	304	304	304	294	
C	295	304	307	305	305	306	295	
D	295	308	307	309	309	310	310	
E	314	311	317	317	---	---	---	
	293 ± 1.5	304 ± 2.0	306 ± 0.8	305 ± 2.5	304 ± 4.5	302 ± 9.2	298 ± 8.0	

*Average ± s.d. of subjects A-D.

resting levels of $3.6 \pm 0.15 \text{ mEq.L}^{-1}$ to $4.4 \pm 0.12 \text{ mEq.L}^{-1}$ by 20% of the duration of the fatiguing exercise. At 40% of the duration to fatigue the average value was $4.9 \pm 0.22 \text{ mEq.L}^{-1}$ remaining at this level throughout the rest of the exercise. These average values during the course of the exercise were not significantly different ($P > 0.05$). Levels of K^+ returned to resting levels within one minute following the end of exercise to $3.5 \pm 0.10 \text{ mEq.L}^{-1}$, even though the forearm blood flow was still high (see Lind & Williams, 1979). It is evident from the data presented in Fig. I.4 that the pattern of release of K from the exercising muscles of the forearm resembled the pattern of forearm blood flow during fatiguing contractions. In contrast, arterial concentrations of K^+ during isometric exercise did not change. Blood samples were withdrawn from the catheter in the brachial artery in 3 subjects and the K^+ levels measured. Resting levels found in the arterial plasma averaged $3.4 \pm 0.17 \text{ mEq.L}^{-1}$. This concentration did not vary much: at half the duration to fatigue, K^+ concentration equalled $3.5 \pm 0.38 \text{ mEq.L}^{-1}$ and at fatigue was $3.5 \pm 0.07 \text{ mEq.L}^{-1}$.

A very different pattern was seen when the changes in ATP concentrations in venous plasma were related to the extent of fatiguing isometric exercise. This relationship is shown in Fig. I.5. The changes in concentration of ATP found in venous blood were multiplied by the forearm blood flow during intermittent contractions at 60% MVC to give total efflux during exercise. While the absolute levels of efflux varied widely from subject to subject, it is obvious that as fatigue was approached, the levels of ATP continuously increased, reaching the highest concentrations and therefore the greatest efflux, since forearm blood flow remained in a steady-state, at fatigue. While the levels of ATP during exercise were quite variable, the resting levels in the forearm from 5 subjects were similar, averaging $35 \text{ pmoles.min}^{-1}.100 \text{ ml}^{-1}$. It is

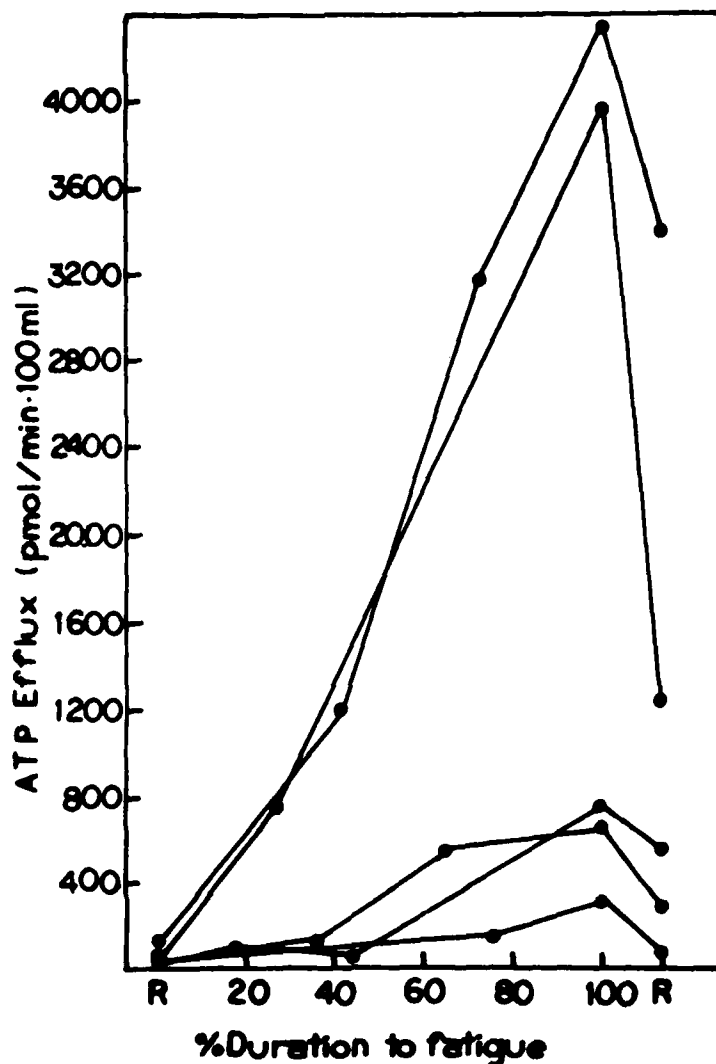


Figure I.5: The increase in the ATP efflux measured in the venous blood from the exercising forearm in relation to the extent of fatiguing intermittent contractions exerted in succession for 4 sec at 60% MVC. The concentration of ATP found in venous plasma was multiplied by each subjects' forearm blood flow to give total efflux, as expressed on the ordinate. Duration of exercise was normalized for each subject. Each curve represents the data measured from a different subject.

important to point out that an efflux of $40-80 \text{ pmoles} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$ seen in all subjects in Fig. I.5 is above the threshold for skeletal muscle vasodilatation (Duff, Patterson & Shepherd, 1963).

The Changes in Arterial and Venous Plasma Catecholamines During Fatiguing Intermittent Hand-Grip Contractions

If there were competition between increasing sympathetic vasoconstriction and metabolic vasodilatation as fatigue developed during these brief isometric contractions, then there ought to be some indicator of the changing sympathetic discharge in the periphery. In an attempt to demonstrate this and to quantify the change in peripheral sympathetic activity, a comparison was made between the concentrations of total plasma catecholamines (adrenalin and noradrenalin) found in the arterial and venous blood. Total catecholamine concentrations were measured in arterial blood samples from 3 of the subjects. These results are shown in Fig. I.6A. Resting levels of catecholamines averaged $25.5 \pm 9.9 \text{ pg} \cdot \text{ml}^{-1}$. There was an increase in the levels of adrenalin and noradrenalin during the course of exercise so that at fatigue, these levels had risen to $159 \pm 43 \text{ pg} \cdot \text{ml}^{-1}$. The concentration of catecholamines declined toward pre-exercise levels within one minute after contractions had ceased, and averaged $54.4 \pm 30.9 \text{ pg} \cdot \text{ml}^{-1}$. In comparison to the very modest change in arterial levels of catecholamines, the changes seen in venous plasma concentrations of catecholamines were much greater. These data are shown for individual subjects in Fig. I.6B. Resting levels of adrenalin and noradrenalin averaged $45.1 \pm 5.4 \text{ pg} \cdot \text{ml}^{-1}$. This level of total catecholamines was not different from the level found in arterial blood ($P > 0.05$). It is evident from Fig. 6B that while the absolute levels of catecholamines vary in different subjects, the same general pattern in the rate of change in concentration of venous catecholamines was demonstrated by each subject. Even during the early part of exercise, at

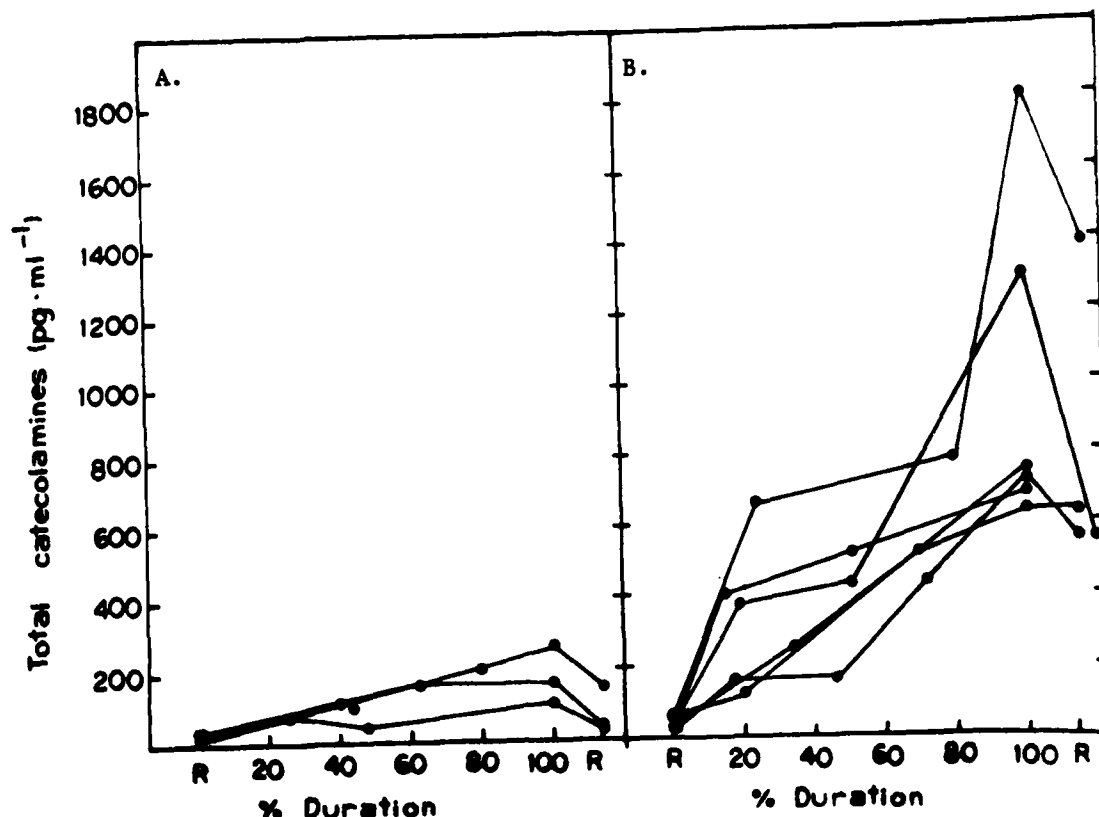


Figure I.6: The concentration, in pg.ml⁻¹, of total catecholamines (adrenalin and noradrenalin) found in arterial plasma (panel A) or venous plasma (panel B) during intermittent contractions at 60% MVC. Exercise was continued until fatigue was reached. Each curve in either section represents the results from individual subjects. In both cases, blood samples were withdrawn from the exercising forearm.

20% of the duration to fatigue, total catecholamines had already increased to 271.5 ± 81.9 pg.ml⁻¹. The highest concentration of catecholamines occurred at fatigue in all of the 5 subjects. This peak averaged 983 ± 258 pg. ml⁻¹. The amounts of these substances found in venous blood samples were 6 times

higher than the concentrations of catecholamines found in arterial blood at fatigue (see Fig. I.6A).

There was a rapid decrease in the concentrations of catecholamines in only 1 min after exercise, as shown in Fig. I.6B, averaging 652 ± 142 pg.ml⁻¹. The rates of change noted for the efflux of ATP and catecholamines across the vascular bed of the muscle were similar. The pattern of release of none of the other vasoactive metabolites was similar to the changes measured in sympathetic output.

If the catecholamines found in venous plasma were to reflect changes in peripheral sympathetic adrenergic activity on skeletal muscle vasculature, then it was important to determine whether there were higher concentrations of adrenalin or noradrenalin present during fatiguing exercise. This determination was performed by thin-layer chromatographic separation of radioactive derivatives of adrenalin and noradrenalin, and the results are shown in Fig. I. 7. Figure I.7A shows the average concentrations of adrenalin found in venous blood samples during the fatiguing intermittent exercise. There was a modest increase in the concentrations of adrenalin from resting levels averaging 77 pg.ml⁻¹ (average of only 2 subjects) to a level averaging 178 ± 47 pg.ml⁻¹ at fatigue. By comparison, there were much higher concentrations of noradrenalin present in venous blood during isometric exercise, ranging from levels of 65 ± 37 pg.ml⁻¹ at rest (average of 3 subjects) to a level of 1001 ± 375 pg.ml⁻¹ at fatigue (average of all 5 subjects).

DISCUSSION

The results of these experiments provide evidence to support the view that during isometric contractions a sympathetic vasoconstriction occurs not only in the vascular beds of the splanchnic, renal (cf. Rowell, 1972) and inactive

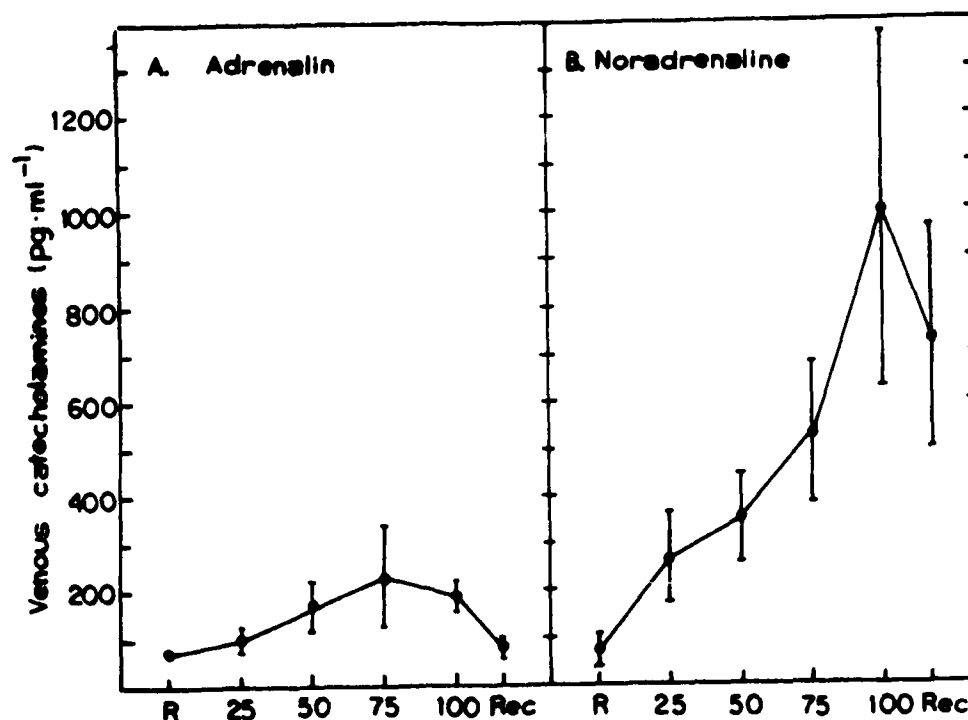


Figure I.7: The average concentration of adrenalin (pg.ml⁻¹) measured from the venous plasma of subjects performing fatiguing intermittent exercise at 60% MVC (panel A). Values were determined from the same blood samples that were withdrawn for the determination of total catecholamines as shown in Fig. 6B. Each point represents the average \pm sem. Panel B shows the average concentration \pm sem of venous plasma noradrenalin found during exercise.

muscular tissue (Blair, Glover & Roddie, 1961; Johnson & Rowell, 1975; Lind & Williams, Section II of this final report) but also to the vessels supplying active muscles (Lind & Williams, 1979). The vasoconstriction is mediated through α -adrenergic mechanisms and occurs in response to contractions as short as 2 sec.

There is no evidence from the data presented here to support the contention that neural vasodilatation of human forearm vessels is exerted by β -adrenergic

mechanisms (Eklund & Kaijser, 1976); following 2-sec contractions, the blood flow increased in direct proportion with the tension, up to 60% MVC, but showed no further increase at higher tensions in both control experiments and following β -blockade. That pattern of response was altered only with α -blockade, when the blood flow following the 2-sec contractions continued to increase linearly at tensions up to 80% MVC, the highest tension examined here. All 3 curves in Fig. 1 are parallel up to 60% MVC indicating that the increase in flow as a result of the brief contractions at different tensions was due to a metabolic dilatation. Similarly, our results following β -receptor blockade during fatiguing intermittent contractions were indistinguishable from those in control experiments both early in the exercise when the blood flow was relatively high and constant, and late during exercise when the flows were the same but the resistance was increasing. It is probable that as subjects continued to exert successive contractions at 60% MVC for 4 sec, forearm resistance increased as neural constrictor traffic increased, reaching its highest activity at or near the point of fatigue. This occurred as part of the somatomotor reflex initiated by the contracting forearm muscles serving to increase the arterial blood pressure (Lind & McNicol, 1967; Abboud, Eckberg, Johannsen & Mark, 1979). We had proposed that metabolites released from contracting muscle competed successfully against the intense vasoconstrictor tone only at the level of pre-capillary sphincters and small arterioles resulting in a forearm blood flow averaging about half the maximal flow possible through the human forearm (Lind & Williams, 1979).

The question remained whether during α -adrenergic blockade blood flow would reach maximal levels at fatigue when mean arterial blood pressure, and therefore, perfusion pressure in the forearm, was highest. Exercise performed when the forearm had been treated with phentolamine did result in maximal or

near-maximal blood flows, reaching $38.7 \pm 1.4 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$.

Challenge of the α -antagonist phentolamine by phenylephrine resulted in the same level of forearm flow as was seen during control conditions, at about only half the maximal level. This evidence supported the concept that sympathetic vasoconstriction occurred in active skeletal muscle (Shepherd, 1966; Barcroft, 1968), and was reinforced by the measurement of venous plasma catecholamines. There was only a modest increase in arterial levels of catecholamines, mostly in the form of adrenalin. This was not unexpected since exercise continued for some 8 min in circumstances resulting in fatigue and high effort when released of adrenal medullary catecholamines would be expected. However, a much larger increase in catecholamines was measured in the venous plasma as the exercise continued, reaching its peak level at fatigue. This corresponded to the postulated increase in neural constrictor tone. Increased release of noradrenalin across the vascular bed of the muscle accounted for most of the venous plasma catecholamine present indicating that α -adrenergic fibres mediated the vasoconstrictor response to the fatiguing muscles. Others have demonstrated changes in plasma catecholamines during various stresses and levels of isometric exercise (Kozlowski, Brzezinska, Kazar, Kowalski & Franczyk, 1973; Watson, Page, Littler, Jones & Reid, 1979).

If our hypothesis were to be correct that small arterioles and pre-capillary sphincters were released from vasoconstrictor influence by the actions of locally produced metabolites, then supporting evidence should be found in the pattern of change in venous concentrations of known vasodilators. Little change occurred in the osmolarity of venous plasma during fatiguing exercise thus it is improbable that osmotically active substances were involved with the vasodilatation seen here (Mellander, et al. 1967); that is not surprising. Venous plasma K^+ on the other hand, increased sufficiently to have a dilator in-

fluence. The role of K^+ as a vasodilator in skeletal muscle exercise hyperemia has been well documented (Kjellmer, 1965; Skinner & Powell, 1967; Haddy & Scott, 1968) and its direct effects on vascular smooth muscle to cause relaxation have been described (Chen, Brace, Scott, Anderson & Haddy, 1972). Kjellmer (1965) found that arterial infusions of K^+ in concentrations 20% above resting levels induced approximately a 30% increase in the blood flow in calf muscles in cats, while concentrations that were 50% above resting levels increased blood flow by approximately 45%. If such findings are applicable to man the increase in K^+ concentration is insufficient to explain the dimension of vasodilatation found in these experiments, although the pattern of the change in venous plasma K^+ seems to correspond quite closely to that seen in the forearm blood flow. Both the K^+ concentration and blood flow increased rapidly from resting levels and remained in a steady-state for the duration of the exercise. However, unlike the post-exercise hyperemia, K^+ levels quickly returned toward resting levels within 1 min after fatigue. It has been suggested from the results from previous studies that K^+ might be the substance released from muscles during sustained isometric contractions which causes the pressor reflex (Lind, McNicol & Donald, 1966; Cotte, Hilton & Perez-Gonzalez, 1972) but the data from the present study do not support this concept. Arterial blood pressure increase during fatiguing intermittent exercise to reach peak values of 160-170 mm Hg for mean pressure. This pressor reflex was similar to that described for sustained fatiguing exercise, both in the manner in which it developed and in the peak levels of pressure attained (Lind & McNicol, 1967; Funderburk, Hipskind, Welton & Lind, 1974). But the pattern of change in K^+ did not correspond to that of arterial blood pressure as it does in sustained contractions (Lind et al. 1966). The present evidence renders it improbable that K^+ can be assigned the role of mediator for the continuously

increasing blood pressure. Because K^+ levels increased initially during fatiguing intermittent exercise and remained in a steady-state, it can be assumed that a constant amount of K^+ was released by each 4 sec contraction and an equally constant amount was washed out of the interstitial space during the 8 sec post-contraction blood flow. The possibility that K^+ can act as a vasodilator by inhibiting adrenergic neurotransmission has been described by others (Lorenz & Vanhoutte, 1975), and this mechanism of action of K^+ cannot be discounted in our findings.

It was quite unexpected that the change in the concentration of ATP correlated with not only the change in the arterial blood pressure but also the change in total venous plasma catecholamines and venous noradrenalin. Adenosine triphosphate has been shown to be released from active skeletal muscle (Abood, Koketsu & Miyamoto, 1962; Boyd & Forrester, 1968) and its role as a vasodilator during exercise has been proposed previously (Forrester & Lind, 1969; Forrester, 1972; Chen, Selleck & Scott, 1972). Duff, Patterson & Shepherd (1963) found that arterial infusion of ATP ($256 \mu\text{g} \cdot \text{min}^{-1}$) induced a forearm blood flow of $22.8 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$. Correcting these amounts for the activity of known plasma ATPases (Holmsen & Holmsen, 1971), these levels would correspond well to the concentrations of ATP found in venous plasma in our experiments. The appearance of ATP in increased amounts during the early part of intermittent exercise reinforces its possible role as a vasodilator during isometric exercise. The fact that ATP was released in increasing concentrations as successive contractions continued and reached its peak concentration at fatigue suggests quite strongly that it may well be the vasodilator substance competing with the increased release of neurotransmitter noradrenalin for the control of the small arterioles and pre-capillary sphincters. Small arteries and larger arterioles removed by distance from those influences would remain under increased vasoconstrictor tone and give rise to the steady-state blood flow seen during the fatiguing exercise. Whether or not ATP has direct effects on vascular smooth muscle is unknown at the present time, although other studies have shown that

application of exogenous ATP relaxes vascular smooth muscle (Afonso, Ansfield, Berndt & Rowe, 1972; Axelsson & Holmberg, 1969; Forrester, Harper, Mackenzie & Thomson, 1979). The possibility that ATP causes vasodilatation by inhibiting adrenergic neurotransmission (Verhaeghe, Vanhoutte & Shepherd, 1977) must certainly be considered as a result of the finding presented here.

II. THE ASSESSMENT OF THE BLOOD FLOW THROUGH INACTIVE MUSCLES IN THE CONTRA-LATERAL LIMB DURING SUSTAINED ISOMETRIC CONTRACTIONS OF ONE FOREARM:

During the last decade, sharply controversial views have been advanced about the blood flow through inactive muscles during isometric contractions of one limb. Eklund and her associates (1972) asserted that a hand-grip contraction was always accompanied by a sharp increase in the blood flow of the contralateral (resting) arm, and, indeed, in the other limbs as well. They believed that that increase in flow in the inactive limbs was mediated by β -adrenergic receptor activity. They discounted their detection of some muscular activity in the "inactive" limbs as being insufficient to account for the changes seen in the blood flow. Their findings directly contradicted those of Lind et al. (1964) who concluded that during a hand-grip contraction there was no increase in blood flow in other limbs in the absence of muscular activity in those limbs.

A similar argument had been associated with rhythmic exercise, although the basic considerations were a little different. Evidence of blood flow through the forearms of subjects exercising their legs was found only early in the exercise and in untrained subjects. In carefully trained subjects, no increase in forearm blood flow was found and the speculation was that in those occasions when an increase was seen during the leg exercise, it was mediated by the cholinergic dilator nerves.

These matters are important because on their correct evaluation depends our understanding of the control of the circulation during exercise - an understanding that is vital to the assessment of successful continuation of muscular function.

The aims of these experiments were to examine with precision the relationship of electromyographic responses to isometric contractions and to use such information to evaluate changes in blood flow in "inactive" muscles in the

contralateral arm during sustained isometric contractions. By use of an α -receptor blockade in the contralateral arm, the influence of increased perfusion pressure during sustained contractions and the effect of sympathetic vasoconstriction were examined.

METHODS

A total of 23 subjects, 16 males and 7 females, volunteered to take part in these experiments. Their ages ranged from 20 to 51 years of age; only one exceeded 35 yr. The methods and procedures to be used were explained in detail to the subjects before they took part; they were all medically examined, including a treadmill stress test (ECG) and a pulmonary function test before they were accepted as subjects. Each signed a statement of informed consent.

Subjects and Training: Seventeen of the subjects were well trained to exert isometric contractions on a hand-grip dynamometer (Clarke et al., 1958). The training procedure involved the exertion of 2 maximal voluntary contractions (MVC), of which the higher was taken to be the MVC. Three min later a series of 5 contractions at sub-maximal tensions (25 to 55% MVC) were held to fatigue, with a 3 min interval between these contractions. This procedure was followed daily for one week and then every other day until the durations of the contractions were repeatable, at 40% MVC to \pm 5%. In the experiments on the contralateral arm, these trained subjects were instructed to relax the arm as well as they could. All experiments on these subjects were repeated.

Six of the subjects were naive and had never before taken part in experiments. The aim of the experiment was not explained to these subjects and during the preparations for the experiments, their attention was drawn to the contracting arm rather than to the contralateral arm. The subjects were not instructed specifically to relax the contralateral arm; two experiments of this kind were done and on a third occasion, the subjects were instructed to relax the arm.

Measurements: The blood flow was measured by the mercury-in-rubber strain-gauge plethysmograph (Whitney, 1953) positioned over the muscular part of the forearm. The distance from the olecranon process was measured on each subject to allow placement in the same position in different experiments. Blood flow was recorded 5 times $\cdot \text{min}^{-1}$. The electromyogram (EMG) was recorded from circular skin electrodes, 9 mm in diameter, held in place with collodion 6 cm apart on the medial surface of the forearm, with the grounding electrode on the upper arm. The skin was scrubbed with acetone to reduce the resistance below 5,000 ohms. The EMG was fed through an integrator, and the amplitude of the root mean square (rms) of the EMG (Lind and Petrofsky, 1979) was recorded on a Honeywell Visicorder. The amplitude of the rms was recorded in arbitrary units, normalized to the value found for each subject in response to an isometric hand-grip contraction at 10% MVC.

In some experiments venous blood samples were taken from a catheter placed in an antecubital vein, and pushed retrogradely into the deep venous plexus of the forearm. The oxygen content of all blood samples were calculated from PO_2 and pH (Radiometer BMS 3 Mk2 and PHM73) and hemoglobin concentration. Oxygen saturations were computed from a standard oxygen dissociation curve corrected for the Bohr effect of 0.49 log PO_2/pH units. The resultant oxygen saturation and hemoglobin concentration enabled the calculation of oxygen contents which were verified in 10% of the samples by gas chromatography. Arterial oxygen contents were estimated from the hemoglobin concentration of the venous samples at 97% oxygen saturation. Arterial blood oxygen saturation has been shown to be unchanged from rest under these experimental conditions (Lind et al., 1964). Oxygen consumption by the forearm muscles was computed from the arterial-venous oxygen difference and the forearm blood flow.

Arterial blood pressure was measured by auscultation in most experiments. In those experiments when subjects had a catheter placed in the brachial artery,

the blood pressure was recorded from a pressure transducer connected to the catheter while blood flows were also being recorded from the contralateral arm.

Procedures: The procedure in all the experiments to measure the blood flow through the contralateral arm was simple. The blood flow was measured in the contralateral forearm for 2 min while the other arm was also at rest, then for 2 min during an isometric contraction at 33% MVC by the other arm and for 2 min following release of the tension. To try to establish whether any increase in blood flow in the contralateral arm was caused by metabolic agents or neurogenic control, the contralateral arm was first "calibrated". At tensions from 1 to 10% MVC, exerted by what was later to be the contralateral arm, the blood flow, amplitude of the rms of the EMG and, in some experiments, the oxygen uptake across the forearm was measured; these low tensions were held for up to 3 min until a steady-state was established for the various physiological measurements. After, there was a rest interval of at least 10 min before the measurements were made on the contralateral (now "calibrated") forearm. In experiments involving "naive" subjects, the "calibration" procedure followed the contralateral arm experiments.

The oxygen uptake across the forearm was measured on 3 of the trained subjects. The blood flow and EMG in the contralateral arm were measured in all 17 trained subjects after "calibration", while the untrained subjects were subjected to a limited "calibration" of the contralateral arm after the contralateral arm experiment had been completed.

Five trained subjects volunteered for experiments in which sympathetic blocking agents were infused into a teflon catheter which had been introduced percutaneously to the brachial artery. The arm which was catheterized became the contralateral arm. Twenty min after catheterization, a control experiment was done. Ten min later, either 1) 0.5 mg REGITINE (Phentolamine) in 5 ml saline was infused over 5-min or 2) 1 mg INDERAL (Propranolol) in 3 ml saline was

infused over 1 min. Five min after completion of the infusion, the contralateral arm experiment was repeated. On a third occasion, 4 of these subjects had both drugs infused, propranolol first, followed by phentolamine in the same dosages; five min later, the experiment was performed.

RESULTS

"Calibration" Results: The results from all the subjects showed that from calibration experiments a linear relationship was found between the isometric force and both the integrated EMG and the steady-state blood flow, as has been described before (Lind et al. 1981). The forearm blood flow took 0.5 to 1.5 min to reach steady-state during sustained isometric contractions at tensions ranging from 1 to 10% MVC.

Contralateral Arm Results: In these experiments the "calibrated" arm became the contralateral arm on which measurements of EMG and blood flow were made when the other arm held an isometric hand-grip at 33% MVC for 2 min. Each experiment was duplicated, and separate, duplicated experiments were held to measure the arterial blood pressure because blood pressures are sometimes difficult to measure in a contracting arm while the measurement of pressures was not feasible on the contralateral arm on which blood flows were measured. The average values of blood flow, mean blood pressure and the peripheral resistance in the forearm of 11 of the well-trained subjects are shown in Fig. II.1; those subjects showed no evidence of muscular activity as judged by the EMG. Nor was there an increase in blood flow through the contralateral arm. At the onset of the contraction there was a tendency for the blood flow to decrease immediately in the contralateral arms of these subjects; that tendency continued so that in the last 30 sec of the isometric contraction the blood flow in the contralateral arm was lower ($p < 0.05$) than it was before the contraction. After the contraction, the blood flow returned quickly to the resting level. At the onset of the

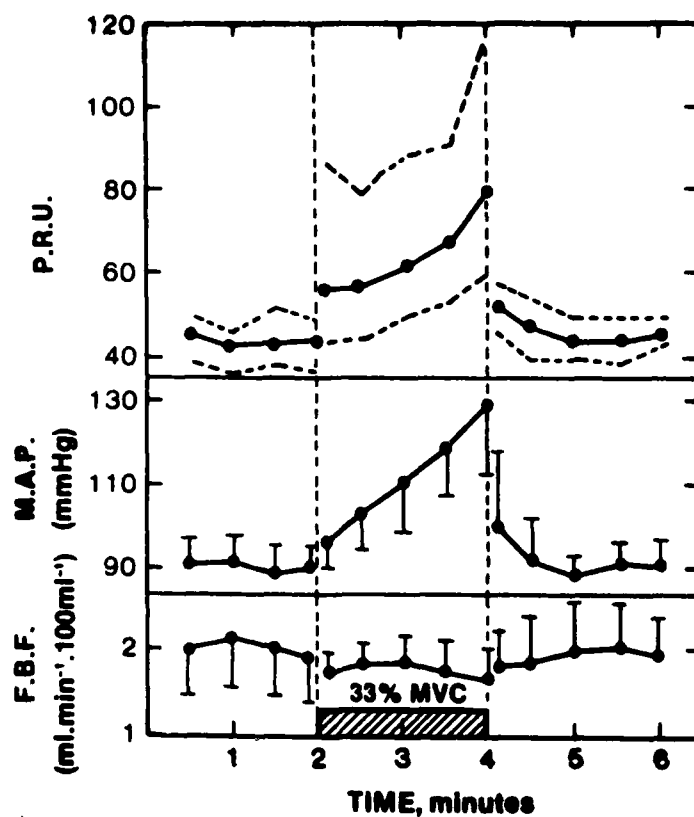


Figure II.1: The contralateral forearm blood flow (FBF), mean arterial blood pressure (MAP) vascular resistance of the forearm (PRU) before, during and after a handgrip contraction at 33% MVC held for 2 min. The symbols represent the average values of 11 trained subjects and the vertical bars represent the SD. For PRU, the range of values is represented by the hatched lines. There was no EMG activity in the contralateral arm of these 11 subjects throughout the experiment.

contraction there was a prompt increase in the mean blood pressure which continued to increase, approximately linearly, as has been described frequently before (cf. Lind et al. 1964). The mean blood pressure also returned rapidly to control values following the contraction. In consequence of these findings,

there was a sharp and prompt increase of vascular resistance in the forearm at the start of the contraction. The resistance increased throughout the contraction, reaching a level nearly double the resting value ($p < 0.01$).

The remaining 6 of the well-trained subjects all showed some EMG activity in the contralateral arm at some time during the isometric contraction. Their average blood flows and EMG values are shown in Fig. II.2; there was a clear relationship between the EMG and the forearm blood flow. However, the individual responses were somewhat variable. Two of the subjects showed a small increase in EMG and blood flow immediately after the contraction began, i.e., for the first 5 to 15 sec; thereafter their muscles were electrically silent and the blood flow returned to resting levels for these 2 subjects for the remainder of the first min. The other 4 of these subjects showed no EMG activity and no increase in blood flow during the first 50 sec of the contraction. An increasing number of these 6 subjects exhibited EMG activity and an increased forearm blood flow at variable times from 50 to 90 sec of the isometric contraction and, after 90 sec of contraction, the EMG and blood flow increased progressively with time for all 6 subjects; any increase in blood flow was always associated with an increase in EMG. For each of these subjects, as the contraction progressed, there were irregular increases of the EMG with roughly matching changes in the blood flow in the contralateral arm. In the inset of Fig. II.2, the solid line represents the average relationship between the EMG activity and blood flow in the earlier "calibration" experiments for these subjects. The symbols in the inset represent the average values for the subjects from the experiment shown in the main part of Fig. II.2, i.e., when the "calibrated" arm had become the contralateral arm. These average values fall rather closely around the "calibration" line. But associated with the point showing the highest blood

flow and the EMG value in the inset in Fig. II.2 is the standard deviation for both the EMG and the blood flow. Obviously, although the average values showed a good correspondence with the "calibration" curve, the individual result could deviate substantially from it, possibly representing a temporal dislocation of

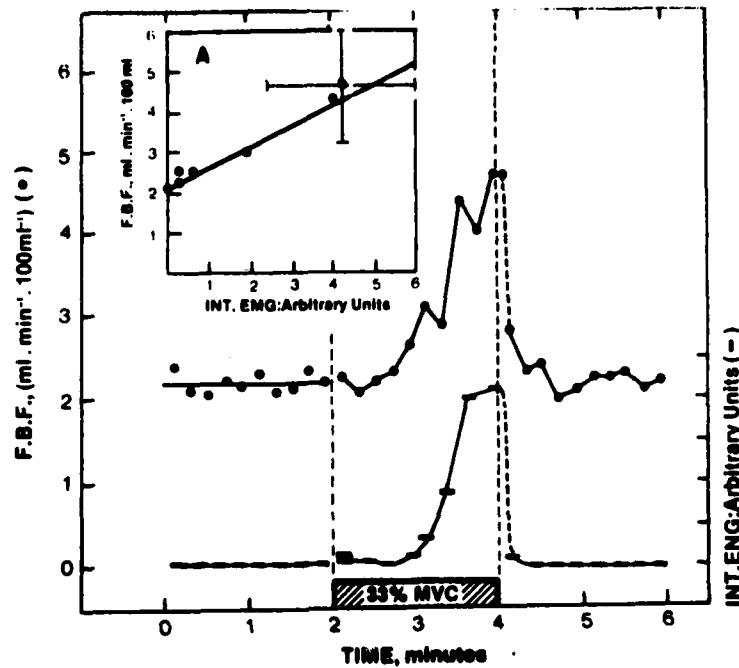


Figure II.2: The average changes in forearm blood flow (●), and integrated EMG (-) of the remaining 6 trained subjects in experiments described on the legend of Fig. 1. In the inset diagram, the solid line shows the relationship between FBF and IEMG for these subjects in the previous "calibration" experiments (when specified handgrip contractions were performed from 1% to 10% MVC; see text for full explanation). The solid symbols in the inset diagram represent the relationship of FBF and IEMG in the main part of the Fig., those values fall closely around the "calibration" line but the SD values for the highest symbol indicate that there was considerable variation in the results.

these two events. The vascular resistance of the forearm increased at first but later decreased below the resting value.

Oxygen Uptake by the Contralateral Forearm: In 3 experiments involving subjects who could not wholly repress muscular activity in the contralateral arm, the EMG and the blood flow increased in the contralateral arm during the isometric contraction. The average O_2 uptake increased from a resting value of $0.22 \text{ ml.}100 \text{ gm. min}^{-1}$ to a peak of $0.63 \text{ ml.}100 \text{ gm. min}^{-1}$ in these subjects, whose blood flow increased from 2.5 ml. min^{-1} to $5.9 \text{ ml.}100 \text{ ml. min}^{-1}$ at the end of the contraction. The EMG values increased during the isometric contraction for all 3 subjects to an average level corresponding to a sustained hand-grip contraction of some 4% MVC when the contralateral arm was "calibrated".

Naive subjects: contralateral arm: In these experiments, the subjects had not experienced physiological experiments of any kind before. Each subject was examined twice without specific instructions to relax the contralateral arm; two of them, who showed EMG activity in the contralateral arm in these experiments were examined a third time when they were instructed specifically to relax the contralateral arm. The average results of the first experiment from 4 of the 6 naive subjects are shown in Fig. II.3. The standard deviations of the average blood flows are given; the range of the peripheral resistance is given. Essentially, these 4 subjects behaved in a similar fashion to the 11 well-trained subjects whose results are shown in Fig. II.1. No EMG activity was detected except for a transient, small increase during the first 15 sec of the contraction on 3 of the 4 subjects; the fourth subject showed no EMG activity at all during the experiment. The average blood flow from all 4 subjects tended to increase in those first few seconds of the contraction; the increased S.D. reflects the variability of the blood flow in the forearms of these naive

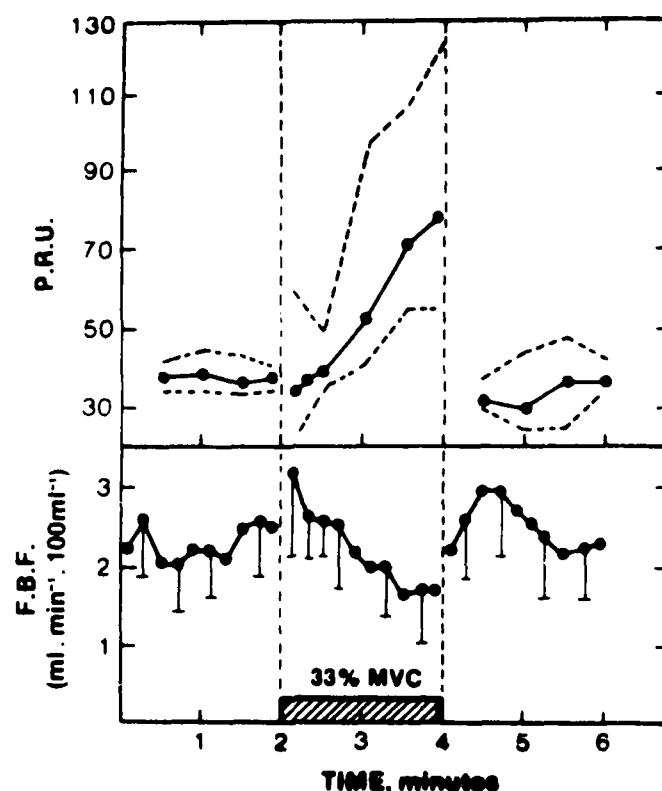


Figure II.3: The average values for FBF and PRU of the contralateral arm of 4 of 5 naive subjects in an experiment similar to that described in Figs. 1 and 2. At the start of the hand-grip contraction there was a small, insignificant increase in FBF (accompanied by a small burst of increase in EMG). Thereafter the FBF declined steadily; there was no measurable EMG. The PRU increased steadily on the contralateral arm. The SD of FBF and ranges of PRU are given.

subjects at that time. Thereafter, the average blood flow fell in an approximately linear manner; during the last 30 sec of the contraction the blood flow was lower ($p < 0.02$) than the resting values for these 4 subjects. After the contraction, the flow returned quickly to resting values - there was a tendency to overshoot the resting value, but it was not statistically significant. The average vascular resistance of the forearm never showed a reduction below the

resting value at any time throughout the contraction; instead, there was a progressive increase in the resistance as the contraction went on.

The remaining two naive subjects showed results that were unique in all these experiments. Immediately on starting the contraction, the blood flow increased by 2 fold, and increased further after 15 sec of contraction to a value 2.5 fold greater than the resting value. Thereafter, the blood flow fell sharply until after 60 sec of contraction it has subsided towards the original, resting level. Following that, the blood flow increased steadily in the second min of the contraction. After the contraction, the blood flow took about 1 min to reach its original resting values, suggesting that a post-exercise hyperemia was involved. Throughout the contraction there was an increased EMG, which showed a sharp increase at the start of the contraction followed by a decline and a subsequent, larger increase. In short, the EMG and blood flow followed a similar course. The vascular resistance of the forearms of these 2 subjects decreased rapidly at the onset of the contraction, increased to about the resting value after one min and then decreased again as the contraction proceeded. Both these subjects were examined a third time, when the observer requested them repeatedly to relax the contralateral arm before and during the isometric contraction. In these experiments, the forearm blood flow did not increase and no EMG activity was detected, while the peripheral resistance increased steadily throughout the isometric contraction, in the same manner as illustrated for trained subjects in Fig. II.1.

Adrenergic Blockade: The average results from 5 well-trained subjects shown in Fig. II.4 represents the blood flow through their contralateral forearms during isometric contractions before and after close arterial infusion of propranolol (Inderal), a β -blocking agent. The mean blood pressures measured from the

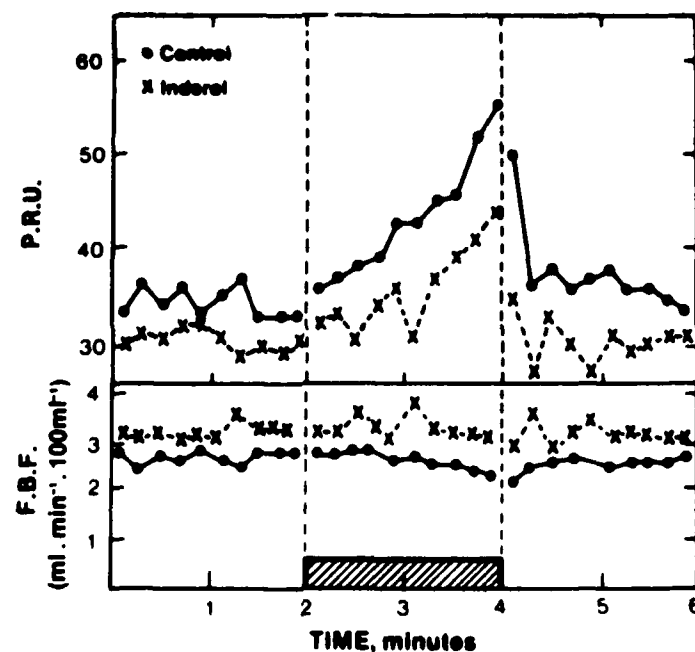


Figure II.4: The average values of FBF and PRu of 5 trained subjects in an experiment similar to that described in the previous Figs. Results from a control (O) experiment and one following close arterial infusion (x) of propranolol (Inderal) in the contralateral arm. The SD is not given here for the sake of clarity; it was similar in dimension to that shown in previous Figs and there was no significant difference in the results shown above.

indwelling arterial catheter followed the same pattern and was of similar dimension to those shown in Fig. II.1, both before and after infusion of Inderal. The average blood flow and vascular resistance of the forearm in the control experiment was similar to that seen in Fig. II.1; in this case, however, the tendency to have a lower blood flow in the contralateral arm during the contraction failed to reach statistical significance. After infusion of

Inderal, the average blood flow tended to be higher than in the control experiment and remained so, in parallel, throughout the experiment. Accordingly, the vascular resistance of the forearm after administration of Inderal tended to be lower than and in parallel to that found in the control experiment. None of the differences in blood flow or vascular resistance were statistically different from those found in the control experiment.

The blood flow through the forearm of the same 5 subjects increased within 3 sec of the start of the infusion into the brachial artery of an α -blocking agent phentolamine (Regitine). For these subjects, after the infusion of Regitine, the forearm blood flow at rest averaged some 9 ml.100 ml.min⁻¹ or about 3 times the control value (Fig. II.5). The subjects' mean blood pressure was similar, throughout the experiment, to those in the control experiment. The blood flow in the contralateral arm rose linearly throughout the isometric contraction to about 15 ml.100 ml.min⁻¹ in these experiments, in association with the increase in perfusion pressure. The vascular resistance of the forearm, which fell markedly following the infusion of Regitine while the forearm was at rest, did not change significantly in the first min of contraction and tended to decrease in the second min of the contraction, but the reduction just failed to reach statistical significance. This possible fall in resistance may have been due to metabolic events (it was not possible to measure the EMG in these experiments) or to dilatation due to circulating catecholamines.

Three of the subjects performed the experiment another time, after infusion of both Inderal and Regitine to block both β - and α -receptors. The results were similar to those when only Regitine had been infused; thus, the tendency for the resistance to fall near the end of the isometric contraction could not have been due to circulating adrenalin because in this experiment the β -receptors were blocked.

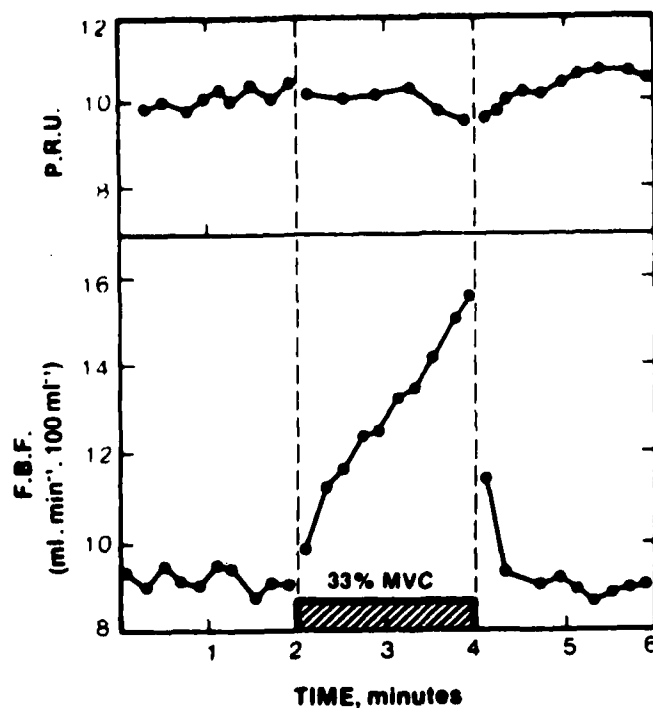


Figure II.5: The average values of FBF and PRU in the contralateral arm of the same 5 trained subjects who yielded the results in Fig. 4, following close arterial infusion of phentolamine (Regitine). The resting blood flow had increased by threefold over the control values (see Fig. 4) and during the hand-grip it increased progressively with the arterial blood pressure. The PRU had reached an average value of about 10 arbitrary units and remained unchanged throughout the experiment.

DISCUSSION

The results of these experiments are clear. During 2 min isometric contractions at 33% MVC the blood flow through the contralateral arm when at rest (i.e., when there was no detectable EMG activity either) decreased in two thirds of the subjects. For the remaining subjects, when the blood flow through the contralateral arm did increase, inadvertent muscular activity was always

detectable as EMG activity and, in 3 subjects who were so tested, by an increase in oxygen usage in the forearm. Those findings confirm those of Lind et al. (1964). They also confirm those of Delius et al. (1972) who reported a diminution in the blood flow in the forearm during unspecified strengths of isometric contractions in other limbs; associated with the reduced blood flow, they reported an increase in sympathetic neural traffic.

The ability to avoid muscular activity in the contralateral arm is under willful control in these experimental conditions, wholly in most subjects and partially in the others. Two thirds of our trained subjects who were instructed to relax the contralateral arm were able to suppress muscular activity altogether while one third could not do so completely. But even in our naive subjects, who were given no specific instructions, some showed no muscular activity at all in the contralateral arm, while some others showed brief and slight activity only at the onset of the contraction. The two remaining naive subjects showed EMG activity in variable amounts throughout the contraction but in later experiments when they were instructed to relax the contralateral arm, they too were able to suppress that activity.

The isometric contractions were always accompanied by an increase in arterial blood pressure, so that in those subjects whose blood flow either did not increase or was reduced, there was an increase in vascular resistance in the contralateral forearm. In those subjects where the blood flow increased in the contralateral arm the vascular resistance in the forearm varied widely, from a slight to a large decrease, depending on the increase in local blood flow (and EMG) and the increase in arterial blood pressure.

In those experiments where blocking agents were infused locally, there was a consistent increase in the vascular resistance during the contraction in both the control experiments and in those in which the β -blockade occurred. The

β -receptors were clearly inert in these experiments. In contrast, following close arterial infusion of an α -blocking agent, the vascular resistance in the contralateral arm was unchanged statistically though it tended to decrease from the resting value during the isometric contraction. In all those experiments, the arterial blood pressure rose by a similar amount during the isometric contractions as they did in the control experiments. The conclusion is inescapable that a vasoconstriction occurs in the contralateral arm during an isometric contraction of another limb, mediated through sympathetic vasoconstrictor fibers. That vasoconstriction may be reduced, abolished or reversed if the muscles in the contralateral arm inadvertently contract.

These findings and conclusions are similar to those from experiments when forearm blood flow was measured during rhythmic leg exercise at levels varying from light to severe and for varying durations up to 60 min (e.g., Blair et al., 1961; Bevegard and Shepherd, 1966; Brod, 1968; Zelis et al., 1969; Wenger et al., 1975; Johnson and Rowell, 1975; Roberts and Wenger, 1979). There is a remarkable unanimity in the conclusions reached from the results of those experiments. In general, with exceptions that are considered below, there is no obvious change in forearm blood flow in response to light leg exercise and a progressive reduction in that flow as the severity of the leg exercise increases. The total forearm blood flow increases later if the exercise is prolonged beyond about 10 min when blood flow is increased in skin vessels, for thermoregulatory purposes. By blocking or anesthetizing the sympathetic nerves separately to skin and to muscle (Blair et al., 1961), by minimizing the skin blood flow by the iontophoresis of epinephrine into the skin (Zelis et al. 1969) and by measuring total forearm blood flow by plethysmography simultaneously with measurement of muscle blood flow by an isotopic procedure (Johnson and Rowell, 1975), it is well established that there is a marked and persistent decrease in

muscle blood flow in the forearm during rhythmic leg exercise. During leg exercise, Blair et al. (1961) measured the blood flow through both forearms, one of which had its deep nerves blocked by anesthetic. The flow through the control arm did not increase and because there was an increase in blood pressure, its vascular resistance increased, whereas in the anesthetized arm, the flow increased with rising blood pressure but its resistance did not. Selective blockade with bretylium tosylate produced the same result as with anesthetic blockade of the deep nerves, confirming that the normal event was controlled by sympathetic constriction.

The results from untrained subjects made these conclusions less clear. Untrained subjects showed a small increase in forearm blood flow. Blair et al. (1961) pointed out that the untrained subjects had difficulty in avoiding arm movements but they were unable to decide whether the slightly increased blood flow was due to the release of metabolic dilators or to sympathetic cholinergic dilatation as Uvnas (1954) had suggested. Bevegard and Shepherd (1966) were similarly uncertain why some of their trained subjects showed a brief and transient (30-60 sec) increase in forearm blood flow at the start of leg exercise. The later workers cited above did not report similar experiences.

Blair et al. (1961) and Dornhorst (1963) found no increase in forearm blood flow during grasping (i.e. isometric) attempts by limbs that were paralyzed, with either gallamine or suxamethonium; the muscular paralysis did not prevent a marked dilation when an emotional stress was presented to the subjects, indicating first that the sympathetic cholinergic pathways were not affected by the paralyzing agents and second, that those pathways contributed little, if anything, to the transient dilation that has been sometimes seen in the forearm

at the start of leg exercise. In this context, a recent publication by Hilton et al, (1979) seems important. They showed, in experiments on cats, that stimulation of the motor cortex resulted in dilation of muscle vessels due solely to the release of metabolic dilators and was not associated with sympathetic cholinergic activity. They pointed out that earlier conclusions of a sympathetically induced vasodilation during exercise "...probably resulted from inadequate control of the stimulus or a failure to recognize weak muscle contractions".

Eklund and her colleagues (1974, 1976, 1978) reported results which were quite different from all those quoted above. They believe that during isometric contractions there is an inevitable increase in blood flow in the contralateral arm, mediated by β -adrenergic receptors. They found sporadic EMG activity in the contralateral arm in the first min and continuous EMG activity in the second min of a 2-min contraction at 33% MVC. But they rejected any causal relationship between the EMG activity and the increased blood flow, despite the fact that the concept that muscular function inevitably leads to a local vasodilation has been accepted since Gaskell's observations in 1880. It has been amply shown in healthy subjects that there is a linear relationship between the degree of muscular activity and the resultant increase in blood flow (Corcondilas et al., 1964; Lind and Williams, 1979, and the present results), as well as in sympathectomized patients (Cordondilas et al., 1964). In addition, Eklund and Kaijser (1976, 1978) reported an increase in the O_2 saturation of blood from deep veins of the contralateral arm, so that calculations from their results, using the Fick principle, show that the oxygen usage of the forearm increased in those experiments, up to double the resting value; increased O_2 uptake across the vascular bed of muscles is commonly associated with muscular activity of those muscles.

The temporal pattern of EMG activity described by Eklund et al. (1974) is somewhat reminiscent of that from those of our own subjects who were unable to suppress muscular activity in the contralateral arm. Further, that pattern fits

the visible evidence from watching uninstructed subjects perform an isometric contraction at 33% MVC. After overcoming the initial inertia of the dynamometer, they find the tension easy to exert at first but later with increasing difficulty, often accompanied with tensing of other limbs. In fact, it is not unusual, in contractions that progress to fatigue, to find the muscles in the contralateral arm so tense that it is hard to measure blood pressure by auscultation on that arm; but on instruction, most subjects can relax the contralateral arm.

Eklund and Kaijser (1974) believed that the increase in blood flow they found was initiated by sympathetic β -receptor activity. But at the onset of isometric exercise after β -receptor blockade, they demonstrated a sharp and prompt decrease in vascular resistance, indicating that some other mechanism was responsible. Since the resistance decreased, it could not be due to -adrenergic activity and, because the β -receptors were blocked, they too, could not have caused the dilatation. The β -receptors are stimulated by epinephrine and therefore are considered to function only when the level of circulating epinephrine increases; there is no known source of epinephrine in skeletal muscle or its vessels. Circulating epinephrine is known to increase as the level of effort increases during isometric exercise (Koslowski, et al, 1973; Watson et al, 1979; Williams et al, 1981), but in only small amounts. Furthermore, because of the time lag of this process involved with the circulation time, the prompt dilatation reported by Eklund and Kaijser (1974) at the onset of a contraction cannot be reasonably explained by the activation of β -receptors.

The accumulation of evidence, which seems to exclude the possibility that sympathetic cholinergic dilatation is a contributor to the functional event, even at the start of exercise, lies heavily in support of a sympathetic vasoconstriction in inactive muscles. Where a prompt increase in blood flow is detected in limbs which are not taking part in the exercise, any dilatation that occurs seems most likely to be explained by inadvertent muscular activity and

and the resultant release of vasodilator metabolites. In experiments where the blood flow to an inactive limb increases after some 10 min of rhythmic exercise, it is the result of dilatation of skin vessels for thermoregulatory purposes; the evidence that the blood flow to inactive muscles does not increase in those conditions is convincing (Johnson and Rowell, 1975).

III. THE INFLUENCE OF RHYTHMIC EXERCISE OF VARYING DURATIONS AND SEVERITIES ON THE ISOMETRIC STRENGTH AND ENDURANCE OF THE EXERCISED MUSCLES:

Most everyday work involves a combination of rhythmic and isometric contractions. It is surprising to find that little attention has been paid either to the interaction of those kinds of exercise on muscular performance or to the evaluation of the "isometric component" of rhythmic exercise.

Recent experiments in this laboratory provide our only real evidence on those interactions (Lind et al. 1982). In descriptive studies, marked reductions in isometric endurance followed rhythmic exercise of different intensities, with an apparently linear relationship. The linearity of the relationship was surprising in view of the fact that the rhythmic exercise included conditions that were undoubtedly anaerobic. Secondly, the extent of the encroachment on isometric endurance, up to 50% was surprising in view of the very short (2.75 min) bouts of rhythmic exercise.

The aims of the present experiments were to explore those relationships further by varying the rhythmic exercise from 20% to 80% $\dot{V}O_2$ max and the duration of that exercise from 1 to 20 minutes; each bout of rhythmic exercise was followed by assessment of the isometric strength and the endurance time of a contraction held at 40% MVC. Investigatory procedures included measurements of heart rate and blood pressure as well as the amplitude of the integrated electromyograph and the muscle temperature.

METHODS AND PROCEDURES

Subjects

Seven healthy young male volunteers acted as subjects. Each subject received a treadmill stress test to ensure that he had no detectable cardiovascular abnormality before taking part in the experiment. The aims and procedures of the experiment were explained to the subjects, and each signed a statement of informed consent.

Training

Each subject trained daily for three weeks his right knee extensor muscles in isometric contractions on a leg dynamometer. Training consisted of exerting 3 maximal voluntary contractions (MVC), each held less than 3 sec., with a 3 min rest period following each MVC. This was followed by 5 sustained contractions at 40% MVC, each held to fatigue, with a 3 minute recovery period after each sustained contraction. The training period was continued until an endurance variation of less than $\pm 5\%$ on 3 consecutive days was achieved.

The training also included 20 min bouts of cycling on a Monark cycle ergometer at approximately 60% of the subject's maximum oxygen uptake ($\text{VO}_2 \text{ max}$) at a cycling rate of 50 rpm. This regimen was followed daily for 2 weeks.

Dynamometer

The leg dynamometer consisted of a solid bench with a hard tempered steel bar attached at one end, some 9" from the floor. On the bar were 4 strain gauges, which formed part of a Wheatstone bridge. At the free end of the steel bar there was a universal joint attached to a leather strap which fitted around the subject's ankle. The subject lay supine with his knees bent over the end of the bench at approximately 90° . The body position of each subject was standardized by placing the back of the lower leg against the edge of the bench while the position of the ankle strap was measured to be in the same position each day.

Oxygen Uptake

The oxygen uptake of each subject was measured while he pedalled on a Monark bicycle ergometer at 50 rpm from zero braking load to loads large enough to induce the subject's maximum oxygen uptake. The belt tension was increased by 4.9 or 9.8 N (0.5 or 1.0 kp) intervals. The volume of expired air was measured on a Parkinson-Cowan dry-gas meter in circuit with a low resistance

mouthpiece. The temperature of the expired air was measured on the exhaust side of the meter. Except for the highest loads, the bicycling was maintained for 4 minutes and gas samples were withdrawn from the output side of the meter during the second half of the second, third and fourth minutes of exercise. At the highest load, a 2-min warming up period was allowed at an intermediate belt tension and when the final belt tension was set, the subject continued exercise until he was exhausted. Each gas sample was analyzed for O_2 on a Servomex O_2 analyzer and for CO_2 on a Goddard capnograph. All respiratory volumes were corrected to STPD values.

Muscle Temperature

Muscle temperature was measured in the lateral aspect of the quadriceps femoris muscle, approximately 20 cm. proximal to the patella, by insertion of a 29-gauge thermocouple needle to a verticle depth of 3 cm. Comparison of observed muscle temperatures of the lateral portion of the muscle between 10 and 20 cm. proximal to the patella have shown there to be no significant difference in temperatures at a given depth (Saltin et al. 1968). For this reason, the position of the thermocouple needle was not precisely controlled, but was placed within an area of some 4 cm² for each subject during all the experiments. The thermocouple needle was inserted only while muscle temperature was being obtained, and was not left in place while exercising. The response time to achieve a stable temperature is within one sec; the needle was left in place for 2-3 sec to ensure a steady-state reading.

Surface Electromyography

Surface electromyography (EMG) was recorded from above the right quadriceps muscle. Two adhesive silver/silver chloride disc electrodes (9 mm diameter) were placed approximately 8 cm apart over the lateral aspect of the quadriceps muscles. Care was taken to ensure that electrode placement was similar for each experiment. The signals were amplified, fed through an RMS integrator and

displayed on a pen recorder. RMS amplitude was determined by drawing the best straight line through 15 sec strips.

Experimental

Type 1: Each experiment consisted of one bout of cycling followed by one isometric contraction of the right (trained) leg held to fatigue at a tension of 40% MVC. Both the work load and duration of bicycling was varied so that experiments were run at 20%, 60% or 80% $\dot{V}O_2$ max for 1, 3, 10 or 20 minutes. The order of the experiments was randomly selected and duplicated on all subjects. Subjects performed no more than one experiment per day. All cycling was at 50 rpm without the use of toe straps. Ambient temperature was controlled 23 - 26°C.

Before cycling, a brief (<3 sec) MVC was exerted by the subject which was used to calculate the 40% MVC target. The subject then rested for 30 minutes. Immediately prior to bicycling, the right quadriceps femoris muscle temperature was obtained. The subject then bicycled at the predetermined work load and duration as described above. Small changes in work position on the cycle saddle have been shown to alter muscle temperature several tenths of a degree (Saltin et al. 1968), so the saddle was adjusted to the same position for each subject for each experiment. Following the bicycling, the subject quickly dismounted the bicycle ergometer and positioned himself in the leg dynamometer. A time interval of 15 sec was allowed for positioning the leg and for acquiring another muscle temperature. The subject then exerted another brief (<3 sec) MVC and allowed the tension to drop quickly to 40% MVC obtained at the start of the experiment and held that tension to fatigue. Heart rates from ECG tracings using standard chest leads, and blood pressures determined by auscultation, were measured at rest, at 1 minute intervals while cycling, as often as possible during the fatiguing isometric contraction, and 1 minute after the isometric contraction (recovery). Surface EMG of the right quadriceps was recorded during

the initial MVC, and continuously during the bicycling, the brief post-bicycling MVC, and throughout the fatiguing contraction.

Type 2: In this group of experiments, carried out on 3 subjects, the quadriceps femoris muscle was passively heated or cooled by immersion of both legs in a water bath. The muscle temperature was measured until a target temperature was achieved, which required immersion up to 30 minutes. Once the desired muscle temperature was obtained, the subject moved to the dynamometer, exerted a brief (<3 sec) MVC, and then held the 40% MVC tension to fatigue as described above. The target muscle temperatures ranged from 34-38°C.

RESULTS

The effect of bicycling on endurance

The isometric endurance times were influenced by both the intensity and duration of bicycling but, after each level of intensity they showed the same pattern with the preceding time of bicycling, falling as the length of the period of bicycling increased from 1 to 10 min. but showing no further reduction as the time was increased to 20 min as shown in Fig. III.1.

When the bicycling was 20% $\dot{V}O_2$ max, the only occasion when the isometric endurance was statistically lower than the control, resting value was after 10 min bicycling. Following bicycling at 60% $\dot{V}O_2$ max for only 1 min, the isometric endurance was reduced to 73% of the control value and fell almost linearly with bicycling time to 51% of the control value after 10 min of bicycling. After only 1 min bicycling at 80% $\dot{V}O_2$ max, the isometric endurance time was only 38% of the control value, while after 10 min bicycling at this severity it was only 17% of the control value.

The same data are plotted in Fig. III.2 in which it can be seen that there was a decremental slope for isometric endurance times which was common to all

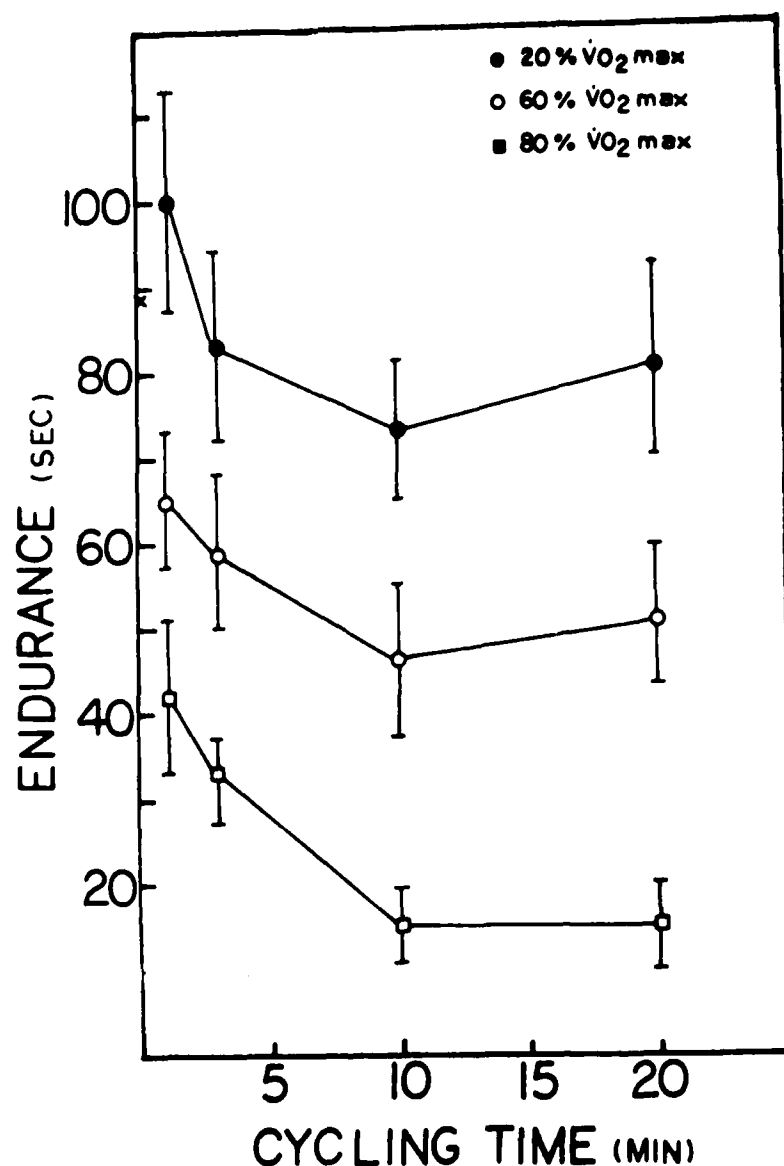


Figure III.1: The average (\pm SD) endurance time of an isometric contraction of the quadriceps at 40% MVC following bicycling for 1 to 20 min at 20, 60 & 80% VO₂ max.

bicycling times when the severity of the rhythmic exercise increased from 20% to 60% VO₂ max, with reductions varying from 0.63 to 0.88 sec·1% VO₂ max⁻¹. As the severity of bicycling increased from 60% VO₂ max to 80% VO₂ max, the decremental slope almost doubled, ranging from 1.20 to 1.71 sec· 1% VO₂ max⁻¹.

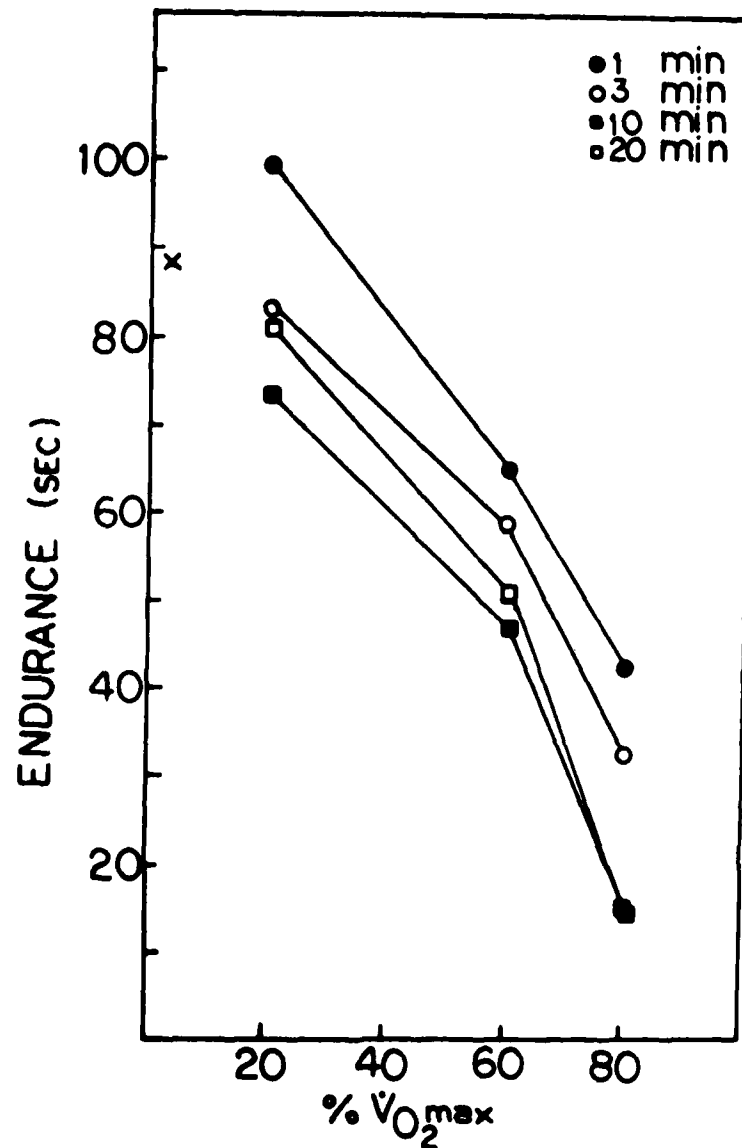


Figure III.2: These data are the same as are shown in Fig. III.1 plotted to show the different ratios of decremental isometric performance following bicycling at rates below and above 60% $\dot{V}O_2\text{max}$.

Muscle temperature and endurance

Resting muscle temperature averaged $36.5 \pm 0.1^\circ\text{C}$ with a range of 34.7 to 37.9°C . Figure III.3 shows the relationship between muscle temperature and bicycling time at the different work loads. Bicycling for 1 min had no

significant effect on the muscle temperature at any work load. After 3 minutes of cycling at 60% and 80% VO_2 max, the muscle temperature showed a significant increase of 1.0°C and 1.3°C , respectively ($p < 0.05$). After 10 minutes of

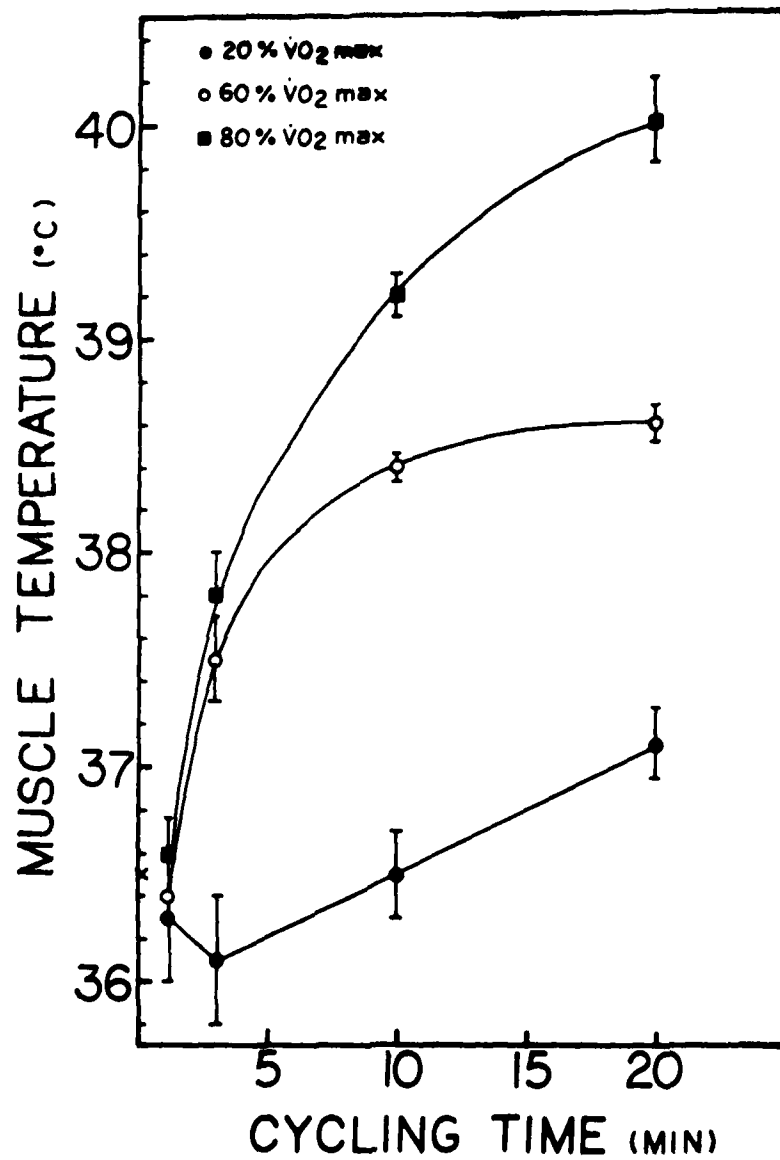


Figure III.3: Changes in the temperature of the quadriceps muscle after bicycling for different lengths of time at 20, 60 & 80% VO_2 max.

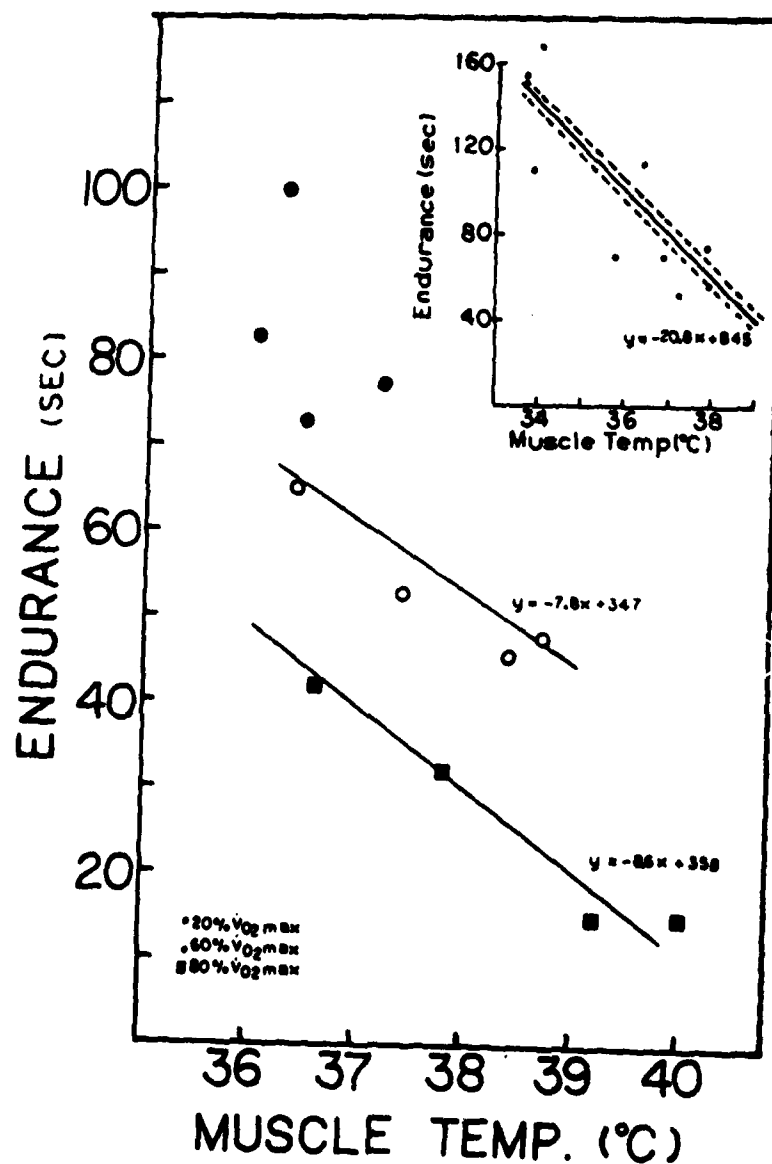


Figure III.4: The relationship between isometric endurance time and the temperature of the quadriceps following rhythmic exercise. The inset in the Fig. represents the relationship between the muscle temperature and endurance in fresh muscle whose temperature was altered by immersion in water.

cycling at 60% VO_2 max, the muscle temperature approached a plateau at 38.6°C, but continued to increase to 40°C in response to cycling at 80% VO_2 max with no evidence of having reached a steady-state. Muscle temperature was not significantly affected by cycling at 20% VO_2 max for 10 min, but after 20 min showed a significant ($p < 0.05$) increase to 37.1°C.

The mean muscle temperature generated by bicycling is correlated with endurance time in Fig. III.4. A discrete inverse, linear relationship exists for each of the two heavier work loads, with correlation coefficients of -0.96 and -0.98 for 60% and 80% VO_2 max, respectively. The isometric endurance time after bicycling at 60% VO_2 max was approximately 20 sec longer than after bicycling at 80% VO_2 max for any observed muscle temperature. The correlation between passively altered muscle temperature and isometric endurance is shown in the inset in Fig. III.4. The observed muscle temperature after passively heating or cooling the leg was in the range of 33.7 to 37.8°C. It was found that the subjects became uncomfortable and the rectal temperature changed significantly from 36.9°C when attempts were made to go beyond this range. An inverse linear relationship was found between passively altered muscle temperature and endurance with a correlation coefficient of -0.80, however, the slope of the passive temperature curve was significantly greater than the slopes of the curves describing exercise-induced changes in muscle temperature and endurance.

Effect of bicycling on muscular strength

The isometric muscle strength after cycling at different work loads and durations showed no ($p > 0.05$) reduction in strength following all durations of 20% and 60% VO_2 max cycling. However, strength was significantly ($p < 0.05$) reduced following all durations of 80% VO_2 max cycling. After only 1 min there was an associated 14% reduction in strength and larger periods of bi-

cycling at this work load caused a progressive and linear reduction in strength to a level that reached 30% below initial strength after 20 min.

When all the data are considered together, Fig. III.5 shows that an inverse linear relationship existed between the muscle temperature and isometric

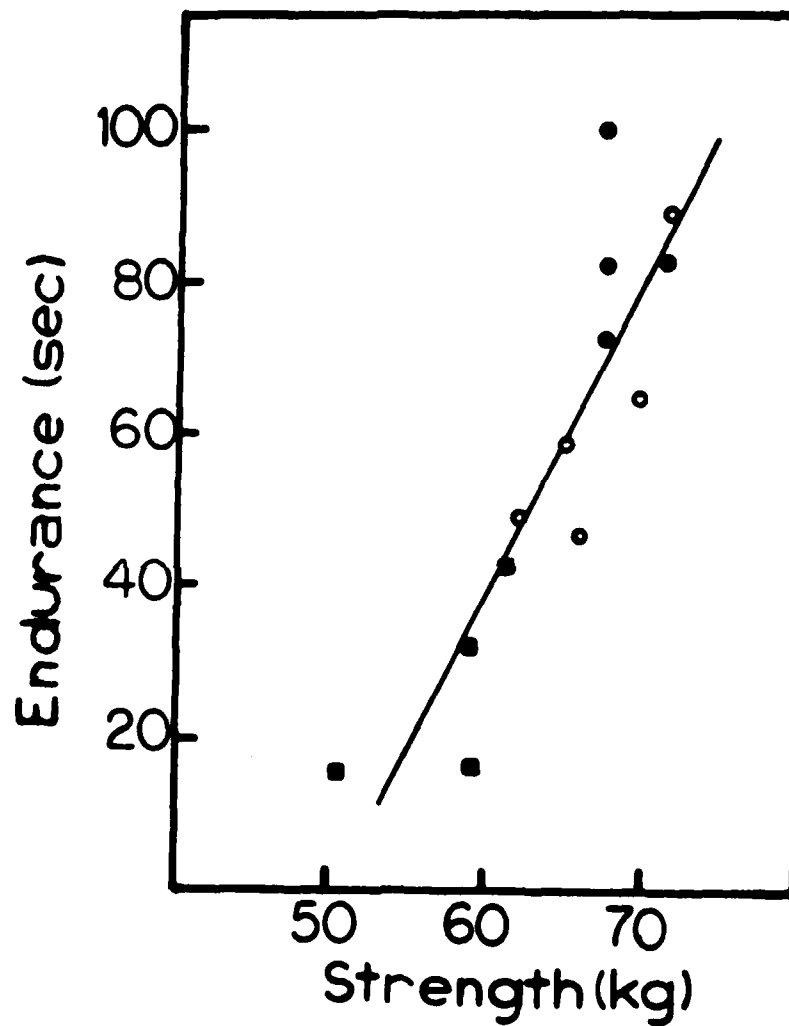


Figure III.5: The relationship of isometric strength following previous rhythmic exercise.

strength after cycling, with a correlation coefficient of -0.83. The association of isometric endurance and strength after cycling is illustrated in Fig. III.6, yielding a direct linear relationship with a correlation coefficient of 0.85.

Electromyographic responses

The RMS amplitude of the surface EMG at the end of each bout of bicycling is shown in Fig. III.7. Since there was some variation in the absolute magnitude of the RMS amplitude, all data are expressed as a percentage of the

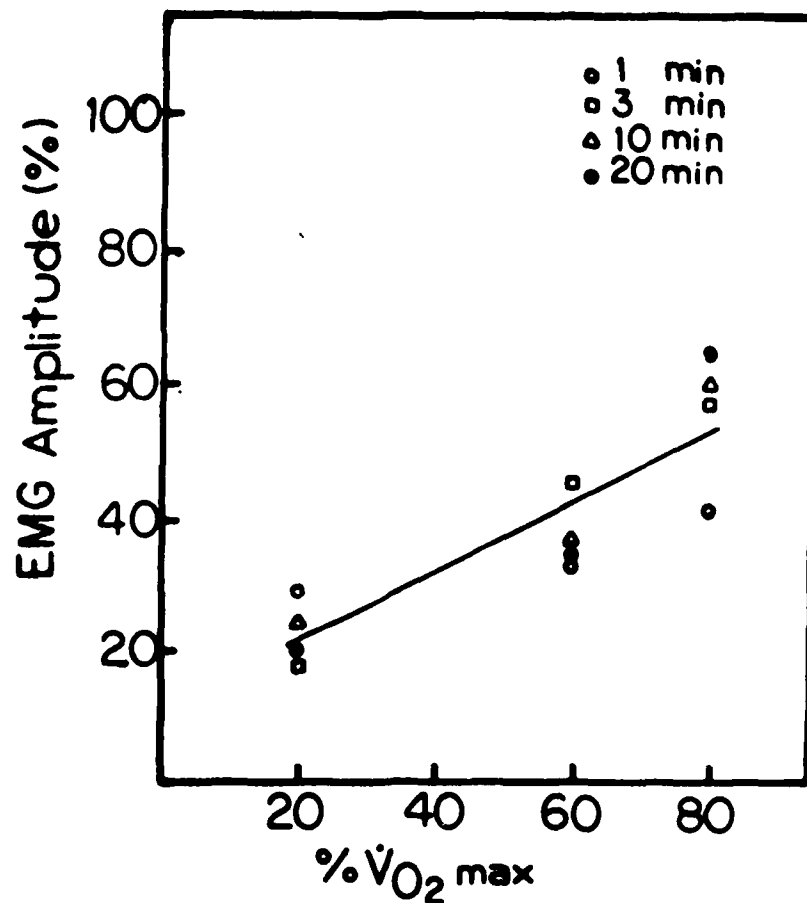


Figure III.6: The relationship between isometric strength and endurance following previous rhythmic exercise.

RMS amplitude achieved from the MVC of the fresh quadriceps prior to any cycling. As expected, the RMS amplitude was directly related to the work load, and appeared unrelated to the duration of bicycling at 20% and 60% VO_2 max. At 80% VO_2 max, there was a non-significant ($p > 0.05$) increase in the RMS amplitude with increasing duration of bicycling, such that at the end of 20 min of cycling, the RMS amplitude reached 65% of that achieved by the isometric MVC, as opposed to value of 41% at the end of only 1 min bicycling at this severity. The RMS value of the EMG amplitude at the point of fatigue from a 40% MVC of a fresh muscle was 54% of that recorded for a brief MVC. The EMG amplitude at the beginning of the contraction was about 40% for the fresh muscle as well as after

low cycling levels. Following the more strenuous cycling, the EMG amplitude at the beginning of the contraction increased such that it was 77% after cycling 20 min at 80% VO_2 max. At fatigue from the sustained contraction, the EMG amplitude was roughly 60%, except after cycling 10 and 20 min at 80 % VO_2 max which resulted in a value of approximately 80%.

The post-cycling strength was significantly decreased following 80% VO_2 max cycling; however, there was no decrease in the RMS value of the surface EMG during the post-cycling MVC.

Cardiovascular responses

Mean blood pressure after cycling was not significantly higher as the work load increased (see levels at 0% fatigue, Fig. III.8). The changes in blood pressure during the contraction was similar regardless of the work load or duration of the preceeding rhythmic exercise. Mean blood pressure always reached 140 - 150 mm Hg at fatigue; some of the data following bicycling at 80% VO_2 max are underestimated because of the difficulty of measuring blood pressure at specific times in such short isometric contractions.

Figure III.8 shows the changes in heart rates throughout each isometric contraction; the heart rates shown at 0% fatigue represent the values during the last 15 sec of bicycling. At the end of any duration of bicycling the heart rate was the same, averaging $91 \text{ beats} \cdot \text{min}^{-1}$. At the end of the subsequent isometric contractions, the average heart rates were not significantly changed. When the subjects exercised at either 60% or 80% $\dot{V}O_2 \text{ max}$ the heart rate at 0% duration increased as the duration of bicycling increased, up to 10 min but there was no further increase as the duration rhythmic exercise increased to 20 min. In all isometric contractions following those levels of bicycling there was a similar pattern, the heart rate falling numerically throughout the contraction; in all cases, the reduction was statistically significant though the degree of significance varied.

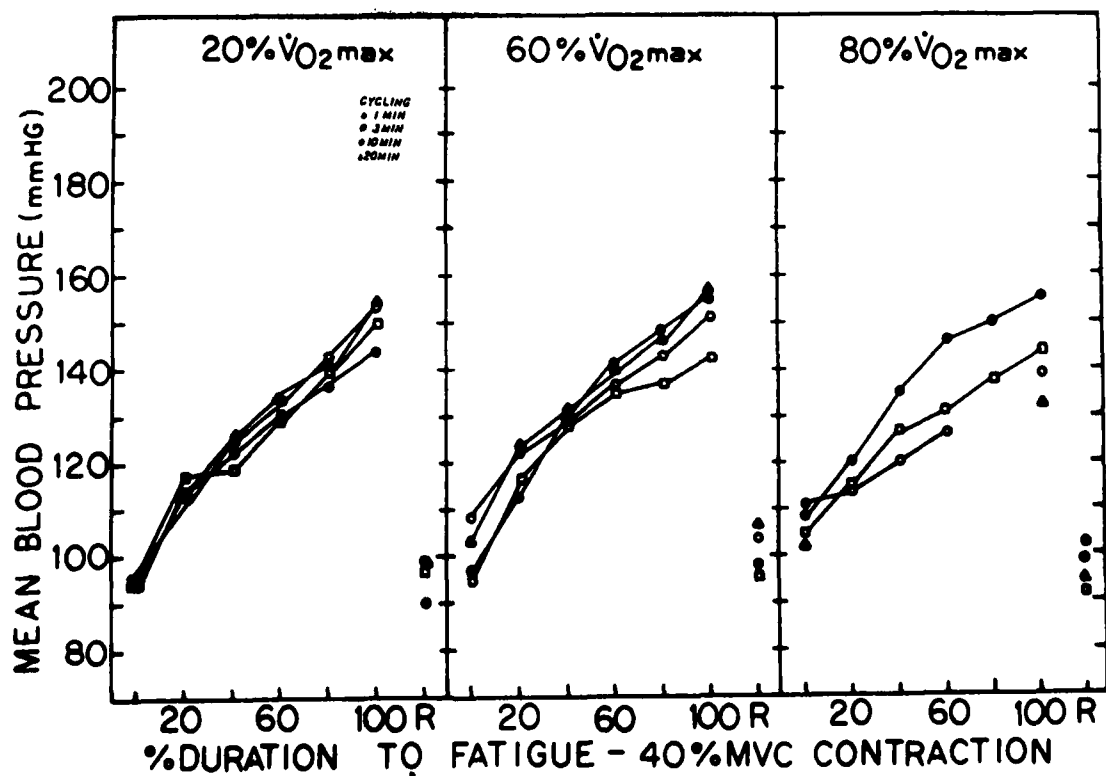


Figure III.7: The RMS amplitude of the surface EMG of the quadriceps in the last 30 seconds of bicycling for different durations and different levels of severity.

Figure III.9 shows that when the heart rate at the end of bicycling is plotted against the severity of the exercise, three linear relationships emerged related to the duration of the exercise. After 1 min bicycling, the heart rate increased at the rate of $0.75 \text{ beats} \cdot \text{min}^{-1} \cdot 1\% \text{ VO}_2 \text{ max}$. When the bicycling was continued for 3 min that value rose to $1.1 \text{ beats} \cdot \text{min}^{-1}$, while after both 10 and 20 min bicycling the value was $1.6 \text{ beats} \cdot \text{min}^{-1} \cdot 1\% \text{ VO}_2 \text{ max}$.

The heart rates at the end of the isometric contractions are plotted against the severity of the severity of the previous rhythmic exercise in Fig. III.11. Again, 3 discreet curves emerged related to the duration of bicycling at 1 min, 3 min and 10-20 min. The relationships were not linear, except following rhythmic exercise for 10 and 20 min, where the increase was at the rate of $1.2 \text{ beats} \cdot \text{min}^{-1} \cdot 1\% \text{ VO}_2 \text{ max}^{-1}$.

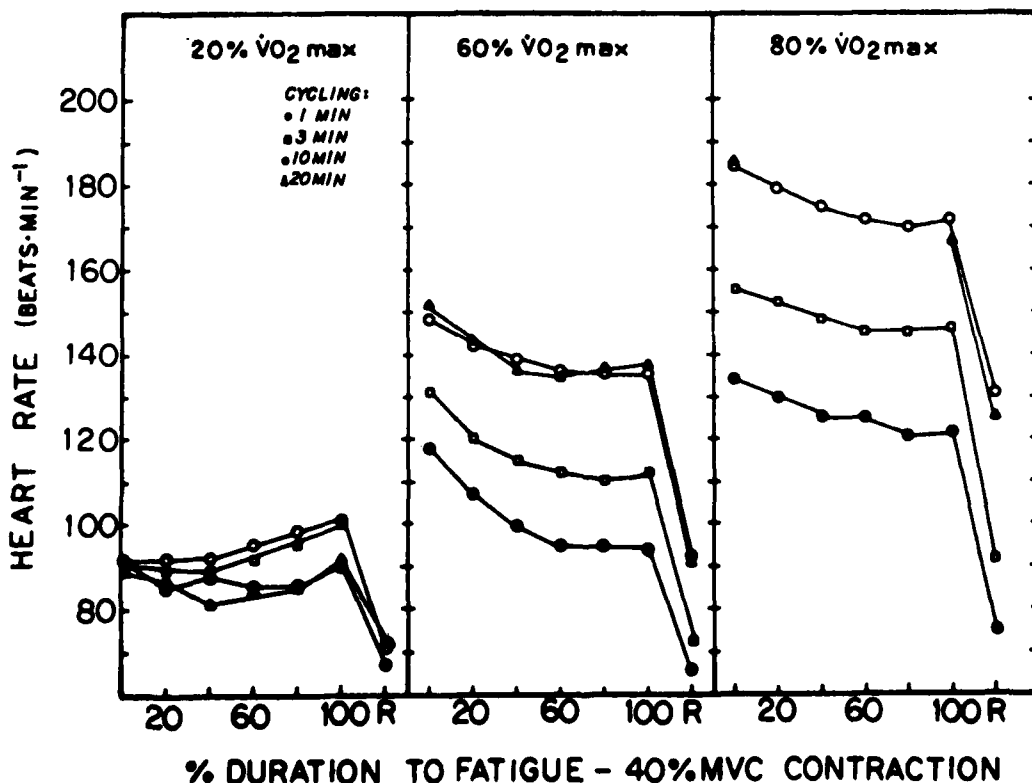


Figure III.8: Changes in mean arterial blood pressure during a sustained isometric contraction at 40% MVC following bicycling of different durations and severity.

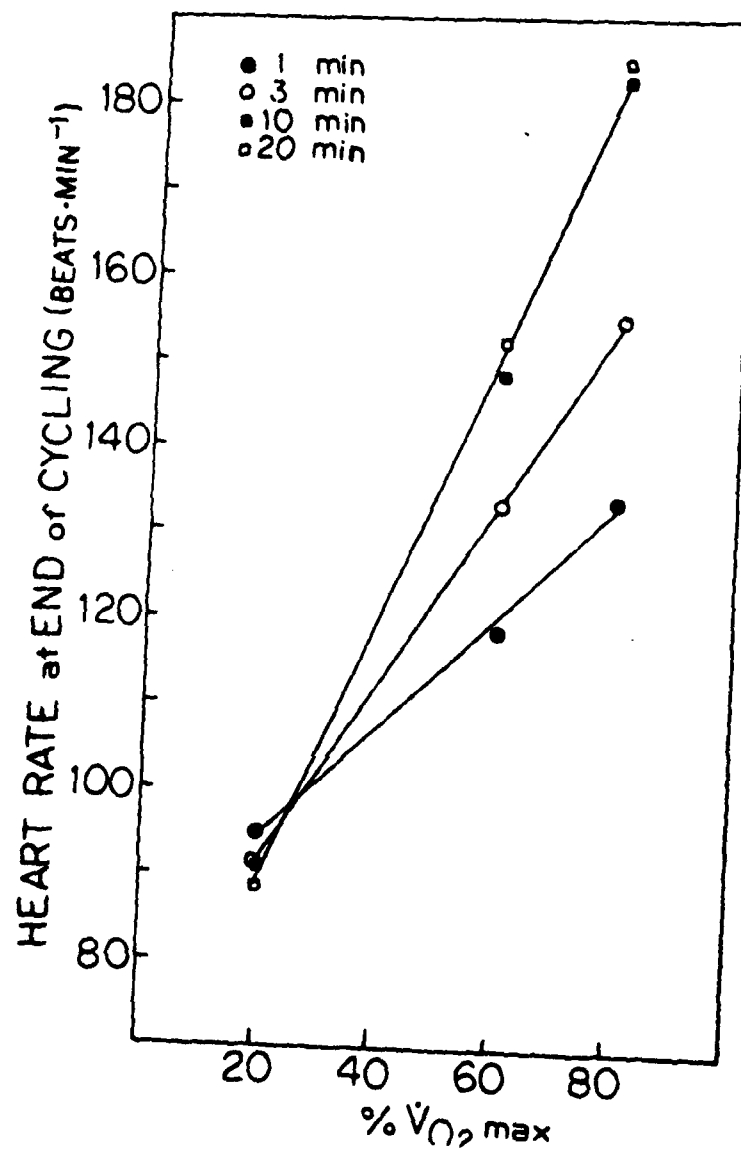


Figure III.9: The changes in heart rate at the end of bicycling for different durations and at 3 levels of severity.

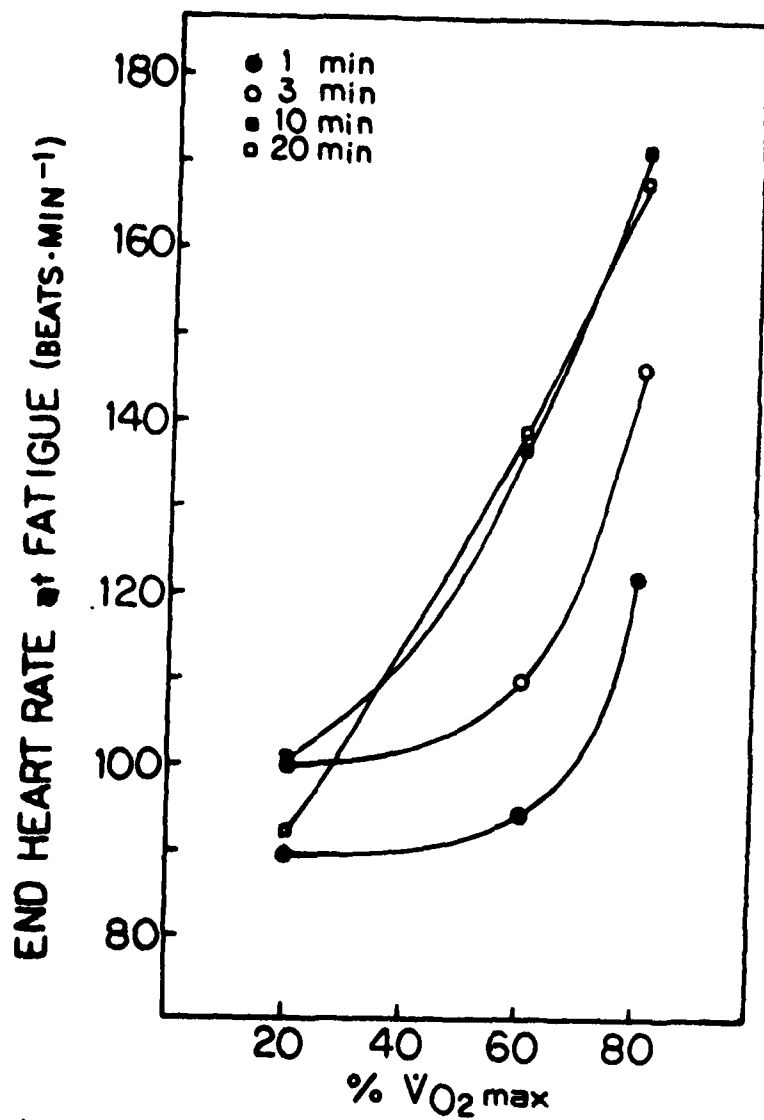


Figure III.10: Changes in the heart rate during a sustained isometric contraction at 40% MVC following bicycling of different durations and severity.

DISCUSSION

In practical terms, the present results re-emphasize the marked influence of preceding rhythmic exercise on the isometric endurance of the exercise muscles. While, in general, the present results follow the pattern reported before with a single duration of the rhythmic exercise, three important differences emerged. First, the reduction in isometric endurance following rhythmic exercise between 20% and 60% VO_2 max occurred at a rate, per 1% VO_2 max, approximately half that found as the rhythmic exercise increased from 60% to 80% VO_2 max. These results are to be expected since the most severe level of exercise would be expected to tax the anaerobic metabolism. There is no clear evidence why this expected finding emerged here but not in the previous experiments; perhaps it is due only to the fact that the earlier experiments involved only 3 subjects with widely variable anthropometric measurements. Second, it was surprising to find that after only one min of rhythmic exercise, the changes in isometric endurance were well established and that the pattern of response with the duration of the rhythmic exercise was so similar. Third, it was unexpected to find, particularly at the higher levels of rhythmic exercise that the decrement of isometric endurance was fully established after 10 min of bicycling and showed no further reduction when the period of rhythmic exercise was extended to 20 min.

There seems little doubt that muscle temperature was a contributory factor to the changes in isometric endurance in these experiments. Muscle temperature was dependent on both the duration and severity of the rhythmic exercise, with a 2-3°C difference between cycling at 20% and 80% VO_2 max for the same duration. This change corresponds exactly to the increments postulated in our

previous study (Lind et al. 1982), but the reduction in endurance was much greater than predicted based solely on this increment of temperature. Muscle temperature was not the sole determinant of isometric endurance since similar temperatures, produced by cycling at different intensities and durations or by passive manipulation, did not result in the same endurance. These data suggest that the higher the intensity of rhythmic exercise, the greater is the isometric component of that exercise. The linear reduction in isometric endurance with passive heating of the muscles has been attributed (Edwards et al. 1972a) to excessive accumulation of muscle metabolites or a reduction in the rate of regeneration of ATP from anaerobic glycolysis below that necessary to maintain the contraction. It seems reasonable to postulate that the reduction in isometric endurance from cycling could be operating through a similar mechanism. However, it is clear from Fig. III.4 that muscle temperature is not solely responsible for the changes in isometric endurance but that some other factor, directly related with the severity of the rhythmic exercise plays a part.

Metabolic activity during isometric contractions at 40% MVC is considered anaerobic since arterial blood supply in the quadriceps is reported to be occluded by mechanical compression of the blood vessels (Edwards et al. 1972b; Saltin et al. 1981). There is some evidence (Karlsson et al. 1975) that at the tensions used in these experiments, increases in lactate could be responsible for isometric fatigue. Metabolic activity during dynamic exercise is considered to be entirely aerobic at levels below 50% VO_2 max, but has an increasing anaerobic component as the work load increases (Karlsson et al. 1971). If lactate or some other muscle metabolite truly is responsible for isometric fatigue under these conditions, then this could explain the drop-off in isometric endurance between 60% and 80% VO_2 max as displayed in Fig. III.2.

Karlsson et al. (1971) have shown that the formation of lactate takes place within the first 2 min of the onset of even submaximal exercise. This evidence indicates that reduced endurance time following exercise at 60% and 80% VO_2 max could very likely occur because of increased accumulation of metabolites or reduced amount of available ATP due to an increasing proportion of metabolic demands being met by anaerobic glycolysis at these work loads. This may also be the explanation for the marked reduction in isometric endurance following 1 min of cycling at the higher workloads. The isometric endurance after exercise at 20% VO_2 max was not different than that found after passively manipulating the muscle temperature. This may merely be indicative of metabolic demands being met entirely by aerobic means and that there was no accumulation of metabolites at this level of dynamic exercise.

The reduction in strength following dynamic exercise is another indication of the isometric component of cycling. A significant decrease in strength was observed only after cycling at 80% VO_2 max, but was demonstrated as early as 1 min of cycling. In the present experiments, strength was found to be linearly related to muscle temperature, but there is good evidence (Clarke et al. 1958) that the strength of the fresh forearm muscle is constant over the range of muscle temperatures found here. The explanation for the present findings involve some elements other than muscle temperature, and is likely due to motor unit fatigue; the relationship shown between strength and muscle temperature in exercised muscles may therefore be more apparent than real. Evidence for this comes from EMG analysis in this study and by Petrofsky (1979), which indicate that the EMG amplitude increases linearly with increasing cycling work loads. These studies show that the EMG amplitude recorded while cycling 1 min at 80% VO_2 max is still less than 60% of the EMG amplitude recorded during a maximal

contraction, but increases to levels over 60% during 20 min of cycling at 80% VO_2 max. This increase in EMG amplitude with work load probably reflects an increase in motor unit recruitment (Petrofsky, 1979). The decline in strength after cycling at 80% VO_2 max was not associated with a decline in the EMG response. Customarily, when there is a fall in tension without a fall in electrical activity, the explanation is placed on failure of the contractile elements in the muscle (Merton 1954; Stephens & Taylor, 1972; Lind & Petrofsky 1979). Therefore, we conclude that the loss of muscular strength after cycling must be attributed to failure in the contractile events in the muscle.

It is clear why the explanation of isometric fatigue has remained elusive. These experiments provide evidence consistent with the theory that metabolic events are the responsible factor for reduction in isometric endurance following dynamic exercise, but we have also implied that the associated loss in muscular strength is attributed to muscle contractile failure. The direct linear relationship of isometric endurance and strength following dynamic exercise, as illustrated in Fig. III.6, indicate that these are probably not entirely independent processes. The full explanation of these findings will obviously require further study.

The cardiovascular responses during static work has been well documented; however, the mechanism responsible for these changes remains under some controversy. Evidence suggests that two separate mechanisms may be involved in the changes of blood pressure and heart rate (Lind et al. 1966; Mitchell et al. 1981) and the data from our present study support this concept. The heart rate was determined predominantly by the level and duration of the rhythmic exercise, suggesting that the isometric exercise required little additional cardiac output. The blood pressure, in contrast, was determined solely by the isometric

contraction of the quadriceps. Its end-point of fatigue was characteristically the same regardless of the preceeding rhythmic exercise and the relative rate of change during the isometric contraction was the same. These findings are consistent with previous studies describing the changes in blood pressure (Funderburk et al. 1974).

REFERENCES

- Abboud, F.M., Eckberg, D.L., Johannsen, V.J., & Mark, A.L. (1979). Carotid and cardiopulmonary baroreceptor control of splanchnic and forearm vascular resistance during venous pooling in man. J. Physiol. 286, 173-184.
- Aboud, L.G., Koketsu, K., & Miyamoto, S. (1962). Outflux of various phosphates during membrane depolarization of excitable tissues. Am. J. Physiol. 202, 469-474.
- Afonso, S., Ansfield, T.J., Berndt, T.B., & Rowe, G.C. (1972). Coronary vasodilator response to hypoxia before and after aminophylline. J. Physiol. 221, 589-600.
- Axelsson, J., & Holmberg, B. (1969). The effects of extracellularly applied ATP and related compounds on electrical and mechanical activity of the smooth muscle taenia coli from the guinea pig. Acta Physiol. Scand. 75: 149-156.
- Barcroft, H. (1968). Blood flow and metabolism in skeletal muscle. In Circulation in Skeletal Muscle ed. Hudlicka. O. Oxford: Pergamon.
- Barcroft, H., Foley, T.H., & McSwiney, R.R. (1971). Experiments on the liberation of phosphate from the muscles of the human forearm during vigorous exercise and on the action of sodium phosphate on forearm muscle blood vessels. J. Physiol. 213, 411-420.
- Barcroft, H., & Swan, H.J.C. (1953). Sympathetic Control of Human Blood Vessels London: Edward Arnold & Co.

- Bevegard, B.S., Shepherd, J.T. (1966). Reaction in man of resistance and capacity vessels in forearm and hand to leg exercise. J. Appl. Physiol. 21, 123-129.
- Blair, D.A., Glover, W.E. & Roddie, I.C. (1961). Vasomotor response in the human arm during leg exercise. Circ. Res. 9, 264-274.
- Bockman, E.L., Berne, R.M. & Rubio, R. (1975). Release of adenosine and lack of release of ATP from contracting skeletal muscle. Pflug. Arch. 355, 229-241.
- Boyd, I.A., & Forrester, T. (1968). The release of adenosine triphosphate from frog skeletal muscle in vitro. J. Physiol. 199, 115-135.
- Brod, J. (1968). In discussion of SM Hilton. Central Nervous Regulation of Skeletal Muscle Circulation p. 13, in Circulation of Skeletal Muscle, ed. Hudlicka. Oxford, Pergamon Press.
- Chen, W.T., Brace, R.A., Scott, J.B., Anderson, D.K., & Haddy, F.J. (1972). The mechanism of the vasodilator action of potassium. Proc. Soc. Exptl. Biol. Med. 140, 820-824.
- Chen, W.T., Sellock, B.H., & Scott, J.B. (1972). Evidence for participation of adenine nucleotides in exercise hyperemia. Fed. Proc. 31, 379.
- Clarke, R.S.J., Hellon, R.F. & Lind, A.R. (1958). The duration of sustained contractions of the human forearm at different muscle temperatures. J. Physiol. 143, 454-473.
- Coote, J.H., Hilton, S.M., Perez-Gonzalez, J.F. (1971). The reflex nature of the pressor response to muscular exercise. J. Physiol. 215, 789-804.
- Cordondilas, A., Koroxenidis, G.T. & Shepherd, J.T. (1964). Effect of a brief contraction of forearm muscles on forearm blood flow. J. Appl. Physiol. 19, 142-146.

- Delius, W., Hagbarth, K.E., Hongell, A., Wallin, B.G. (1972). Maneuvers affecting sympathetic outflow in human nerves. Acta Physiol. Scand. 84, 82-94.
- Donald, D.E., Rowlands, D.J., & Ferguson, D.A. (1970). Similarity of blood flow in the normal and the sympathectomized dog hindlimb during graded exercise. Circ. Res. 26, 185-199.
- Dornhorst, A.C. (1963). Hyperemia induced by exercise and ischemia. Brit. Med. Bull. 19, 37-140.
- Duff, F., Patterson, G.C., & Shepherd, J.T. (1963). A quantitative study of the response to adenosine triphosphate of the blood vessels of the human hand and forearm. J. Physiol. 125, 581-589.
- Edwards, R.H.T., Harris, R.C., Hultman, E., Kaijser, L., Koh, D., and Nordesjo, L-O. (1972a). Effect of temperature on muscle energy metabolism and endurance during successive isometric contractions, sustained to fatigue, of the quadriceps muscle in man. J. Physiol. 220, 335-352.
- Edwards, R.H.T., Hill, D.K., and McDonnell, M. (1972b). Myothermal and intramuscular pressure measurements during isometric contractions of the human quadriceps muscle. J. Physiol. 224, 58-59P.
- Eklund, B., & Kaijser, L. (1976). Effect of regional α - and β -adrenergic blockade on blood flow in the resting forearm during contralateral isometric handgrip. J. Physiol. 262, 39-50.
- Eklund, B., & Kaijser, L. (1978). Blood flow in the resting forearm during prolonged contralateral isometric handgrip at maximal effort. J. Physiol. 277, 359-366.
- Eklund, B., Kaijser, L. (1974). Blood flow in resting (contralateral) arm and leg during isometric contraction. J. Physiol. 240, 111-124.

- Forrester, T. (1972). An estimate of adenosine triphosphate release into the venous effluent from exercising human forearm muscle. J. Physiol. 244, 611-628.
- Forrester, T., Harper, A.M., Mackenzie, E.T., & Thomson, E.M. (1979). Effect of adenosine triphosphate and some derivatives on cerebral blood flow and metabolism. J. Physiol. 296, 343-355.
- Forrester, T., & Lind, A.R. (1969). Identification of ATP in human plasma and the concentration in the venous effluent of forearm muscles before, during and after sustained contraction. J. Physiol. 204, 347-364.
- Funderburk, C.F., Hipskind, S.G., Welton, R.C., & Lind, A.R. (1974). Development of and recovery from fatigue induced by static effort at various tensions. J. Appl. Physiol. 37, 392-396.
- Gaskell, W.H. (1877). Further researches on the vasomotor nerves of ordinary muscles. J. Physiol. 1, 262-302.
- Haddy, F.J., & Scott, J.B. (1968). Metabolically linked vasoactive chemicals in local regulation of blood flow. Physiol. Rev. 48: 688-707.
- Hilton, S.M. (1953). Experiments on the post-contraction hyperemia of skeletal muscle. J. Physiol. 120, 230-245.
- Hilton, S.M. (1977). Evidence for phosphate as a mediator of functional hyperemia in skeletal muscles. Pflug. Arch. 369, 151-159.
- Hilton, S.M., Syper, K.M., & Timms, R.J. (1979). The origin of the hindlimb vasodilatation evoked by stimulation of the motor cortex in the cat. J. Physiol. 287, 545-557.
- Holmsen, I., & Holmsen, H. (1971). Partial purification and characterization of an ADP phosphorylase from human plasma. Thromb. Diath. Haemorrh. 26, 177-191.
- Honig, C.R., & Frierson, J.L. (1976). Neurons intrinsic to arterioles initiate post-contraction vasodilatation. Am. J. Physiol. 230, 493-507.

- Johnson, J.M., Rowell, L.B. (1975). Forearm skin and muscle vascular responses to prolonged leg exercise in man. J. Appl. Physiol. 39, 920-924.
- Karlsson, J. (1971). Lactate and phosphagen concentrations in working muscle of man. Acta Physiol. Scand. Suppl. 358.
- Karlsson, J., Funderburk, C.F., Essen, B., and Lind, A.R. (1975). Constituents of human muscle in isometric fatigue. J. Appl. Physiol. 38(2), 208-211.
- Kjellmer, I. (1965). Potassium ion as a vasodilator during muscular exercise. Acta Physiol. Scand. 63, 460-468.
- Kozlowski, S., Brezezinska, Z., Nazar, K., Kowalski, W., & Franczyk, M. (1973). Plasma catecholamines during sustained isometric exercise. Clin. Science Mol. Med. 45, 723-731.
- Lind, A.R., Dahms, T.E., Williams, C.A., Petrofsky, J.S. (1981). Blood flow through the "resting" arm during hand grip contractions. Circ. Res. 48: Suppl. I, 1104-1109.
- Lind, A.R., & McNicol, G.W. (1967). Local and central circulatory responses to sustained contractions and the effect of free or restricted arterial inflow on post-exercise hyperemia. J. Physiol. 192, 575-593.
- Lind, A.R., McNicol, G.W., & Donald, K.W. (1966). Circulatory adjustments to sustained (static) muscular activity. Proc. Sympos. Physical Activity in Health and Disease. Oslo: Universitets-forlaget, 39-63.
- Lind, A.R., Petrofsky, J.S. (1979). The amplitude of the surface electromyogram during fatiguing isometric contractions. Muscle and Nerve 2, 257-264.
- Lind, A.R., Rochelle, R.R., Rinehart, J.S., Petrofsky, J.S., & Burse, R.L. (1982). Isometric fatigue induced by different levels of rhythmic exercise. Eur. J. App. Physiol. 49, 243-254.
- Lind, A.R., Taylor, S.H., Humphreys, P.W., Kennelly, B.M., & Donald, K.W. (1964). The circulatory effects of sustained voluntary muscle contractions. Clin. Sci. 27, 229-244.

- Lind, A.R., & Williams, C.A. (1979). The control of blood flow through human forearm muscles following brief isometric contractions. J. Physiol. 288, 529-547.
- Lorenz, R.R., & Vanhoutee, P.M. (1975). Inhibition of adrenergic neurotransmission in isolated veins of the dog by potassium ions. J. Physiol. 246, 479-500.
- Mellander, S., Johansson, B., Gray, S., Jonsson, O., Lundvall, J., & Hjuing, B. (1976). The effects of hyperosmolarity on intact and isolated vascular smooth muscle. Possible role in exercise hyperemia. Angiology 4, 310-322.
- Merton, P.A. (1954). Voluntary strength and fatigue. J. Physiol. 123, 553-564.
- Mitchell, J.H., Blomqvist, C.G., Lind, A.R., Saltin, B., & Shepherd, J.T., Editors. (1981). Static (Isometric) Exercise: Cardiovascular Responses and Neural Control Mechanisms. Circ. Res. 48 (Suppl. 1): American Heart Association.
- Passan, P.G., & Peuler, J.D. (1973). A simplified radiometric assay for plasma norepinephrine and epinephrine. Anal. Biochem. 51, 618-631.
- Petrofsky, J.S. (1979). Frequency and amplitude analysis of the EMG during exercise on the bicycle ergometer. Eur. J. Appl. Physiol. 41, 1-15.
- Roberts, M.F., & Wenger, C.B. (1979). Control of skin blood flow during exercise: thermal and nonthermal factors. J. Appl. Physiol. Respirat. Environ. Exercise Physiol. 46, 780-786.
- Saltin, B., Gagge, A.P., and Stolwijk, J.A.J. (1968). Muscle temperature during submaximal exercise in man. J. Appl. Physiol. 25(6), 679-688.
- Saltin, B., Sjogaard, G., Gaffney, F.A., & Rowell, L.B. (1981). Potassium, lactate, and water fluxes in human quadriceps muscle during static contractions. Circ. Res. 48 (Suppl. 1), 18-24.

- Shepherd, J.T. (1967). Behavior of resistance and capacity vessels in human limbs during exercise. Amer. Heart Assoc. Monograph No. 15, 70-82.
- Skinner, N.S. & Powell, W.J. (1967). Action of oxygen and potassium on vascular resistance of dog skeletal muscle. Am. J. Physiol. 212, 533-540.
- Stephens, J.A., & Taylor, A. (1972). Fatigue of maintained voluntary muscle contraction in man. J. Physiol. 220, 1-18.
- Uvnas B. (1954). Sympathetic vasodilator outflow. Physiol. Rev. 34, 608-632.
- Verghaeghe, R.H., Vanhoutee, P.M., & Shepherd, J.T. (1977). Inhibition of sympathetic neurotransmission in canine blood vessels by adenosine and adenine nucleotides. Circulation Res. 40, 208-215.
- Watson, R.D.S., Page, A.J.F., Littler, W.A., Jones, D.H. & Reid, J.L. (1979). Plasma noradrenaline concentrations at different vascular sites during rest and isometric and dynamic exercise. Clin. Sci. 57, 545-547.
- Wenger, C.B., Roberts, M.F., Stolwijk, J.A.J., & Nadel, E.R. (1975). Forearm blood flow during body temperature transients produced by leg exercise. J. Appl. Physiol. 38, 58-63.
- Witney, R.J. (1953). The measurement of volume changes in human limbs. J. Physiol. 121, 1-27.
- Williams, C.A., Mudd, J.C., & Lind, A.R. (1981). The forearm blood flow during intermittent hand grip isometric exercise. Circ. Res. 48 (Suppl. I), 110-117.
- Zelis, R., Mason, D.T., & Brunwald, E. (1969). Partition of blood flow to the cutaneous and muscular beds of the forearm at rest and during leg exercise in normal subjects and in patients with heart failure. Circ. Res. 24, 799-806.

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